INTERNATIONAL RECORD OF MEDICINE

VOLUME 173 NO. 6 | JUNE 1960

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

Odd Electron Structures in the Concept of "Metabolic Resuscitation": Therapeutic Introduction in Neuropharmacology and Psychopharmacology — H. Laborit, J. Drouet, J. Gerard, J. M. Jouany, C. Narvaez, P. Niaussat, and B. Weber

Personnel Decontamination Units at Brookhaven National Laboratory — R. A. Love

The Protective Value of the Middle Ear Reflex — David A. Hilding and John L. Fletcher

A Clinical Evaluation of Fluphenazine — William D. Gray

Notes on the Hallucinogenic State — Sidney Cohen

On an Armenian "Flying Carpet" — Felix Marti-Ibañez

Reviews

International Clinical Newsletter

NEW ENLARGED

QUARTERLY REVIEW OF OPHTHALMOLOGY
(For the Medical Profession)
Conrad Berens, M.D., Editor-in-Chief
Arnold S. Breakey, M.D., Executive Editor

A JOURNAL OF MD PUBLICATIONS, INC.

Two exciting new

SIGERIST

ANTHOLOGIES

available as a set, handsomely boxed, at the special combination price of $10

HENRY E. SIGERIST ON THE HISTORY OF MEDICINE

Edited by Félix Martí-Ibáñez, M.D. / Foreword by John F. Fulton, M.D.

In twenty-seven highly diversified essays and articles, Sigerist presents an entertaining and enlightening view of the history of medicine. This carefully selected collection spans the time from the beginning of the practice of medicine to the present, vividly portraying the events and the men who have made medical history. In presenting his major concepts and ideas within the framework of these writings, Sigerist reveals himself as the wit, scholar, and great historian that he was.

316 PAGES / CLOTH BOUND / $6.75

HENRY E. SIGERIST ON THE SOCIOLOGY OF MEDICINE

Edited by Milton I. Roemer, M.D. / Foreword by James M. Mackintosh, M.D.

The views and concepts of Sigerist on medical sociology have never been more clearly nor comprehensively presented than in this anthology of thirty-one essays and articles. This volume contains the essence of his theories on the sociology of medicine and the best of his medico-sociological writings. Within these pages Sigerist exhibits his extreme concern for the future of medicine and of mankind and reveals himself as a supreme humanist and individualist. This fascinating collection provides an extraordinary insight on the changing world of medical sociology.

400 PAGES / CLOTH BOUND / $6.75

MD
PUBLICATIONS, INC.
New York

Please send me the following books:

___HENRY E. SIGERIST ON THE HISTORY OF MEDICINE $6.75

___HENRY E. SIGERIST ON THE SOCIOLOGY OF MEDICINE $6.75

___**Both books at the special combination price of $10.00**

NAME .....
(PLEASE PRINT)

ADDRESS .....

CITY ..... ZONE .... STATE .....

☐ CHECK ENCLOSED
☐ BILL ME
(If payment is enclosed, we will pay postage.)

MD PUBLICATIONS, INC. *30 E. 60th Street, N.Y. 22, N.Y.*

INTERNATIONAL RECORD OF MEDICINE

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

A JOURNAL OF ADVANCED EXPERIMENTAL AND CLINICAL REPORTS

FELIX MARTI-IBAÑEZ, M.D., Editor-in-Chief
Professor and Chairman of the Department of the History of Medicine,
New York Medical College, Flower and Fifth Avenue Hospitals, New York, N.Y.

VOL. 173 NO. 6 *WHOLE NUMBER 2928* *JUNE 1960*

The *International Record of Medicine*® is published monthly by MD Publications, Inc. (30 E. 60th Street, New York, N. Y., Félix Martí-Ibáñez, M.D., President). ©Copyright 1960 by MD Publications, Inc. Entered as second class matter at 5800 N. Marvine Street, Philadelphia, Pa. Matter appearing in *International Record of Medicine* is covered by copyright. The reproduction of articles (or parts of articles) appearing in *International Record of Medicine* is not permitted. Permission must be received in writing from the editor for reprinting material in whole or in part. Subscription Rate: $11.00 for one year, $28.00 for three years.

EDITORIAL BOARD

FELIX MARTI-IBAÑEZ, M.D., Editor

NATIONAL EDITORIAL BOARD

FRED L. ADAIR, M.D., *University of Chicago*

HARRY L. ARNOLD, JR., M.D., *Editor, Hawaii Medical Journal, Honolulu, Hawaii*

W. WAYNE BABCOCK, M.D., *Temple University*

HOWARD C. BALLENGER, M.D., *Northwestern University*

CONRAD BERENS, M.D., *The Ophthalmological Foundation*

ALEXANDER W. BLAIN, M.D., *Wayne University*

ALFRED BLALOCK, M.D., *Johns Hopkins University*

W. F. BRAASCH, M.D., *Mayo Clinic*

ROBERT H. BROH-KAHN, M.D., *New York, N. Y.*

MORTON S. BRYER, M.D., *The Mount Sinai Hospital*

LEROY A. CALKINS, M.D., *University of Kansas*

NORTON CANFIELD, M.D., *New Haven, Conn.*

BAYARD CARTER, M.D., *Duke University*

RUSSELL L. CECIL, M.D., *Cornell University*

F. CO TUI, M.D., *Creedmoor Institute*

FREDERICK A. COLLIER, M.D., *University of Michigan*

WILLARD R. COOKE, M.D., *University of Texas*

WALTER T. DANNREUTHER, M.D., *New York University*

CLYDE L. DEMING, M.D., *Yale University School of Medicine*

R. S. DINSMORE, M.D., *Cleveland Clinic*

HENRY DOLGER, M.D., *New York, N. Y.*

I. E. DRABKIN, PH.D., *The College of the City of New York*

DANIEL C. ELKIN, M.D., *Emory University*

LUDWIG A. EMGE, M.D., *Stanford University*

HAROLD K. FABER, M.D., *Stanford University Hospital*

HARRY A. FELDMAN, M.D., *State University of New York*

JOSEPH H. FOBES, M.D., *New York Medical College*

WILLIS D. GATCH, M.D., *University of Indiana*

LOUIS J. GELBER, M.D., *Rockville Center, L. I., N. Y.*

DAVID GROB, M.D., *Johns Hopkins Medical School*

BERNARD J. HANLEY, M.D., *University of Southern California*

FRENCH K. HANSEL, M.D., *Washington University*

CLYDE A. HEATLY, M.D., *University of Rochester*

FRANK HINMAN, M.D., *University of California*

CLARENCE B. INGRAHAM, M.D., *University of Colorado*

J. BAY JACOBS, M.D., *Georgetown University*

HARRY H. KERR, M.D., *George Washington University*

WILLIAM J. KERR, M.D., *Blue Lake, California*

I. NEWTON KUGELMASS, M.D., *New York, N. Y.*

DEAN M. LIERLE, M.D., *University of Iowa*

IRVINE MCQUARRIE, M.D., *Oakland, Calif.*

RALPH H. MAJOR, M.D., *University of Kansas*

ALTON OCHSNER, M.D., *Tulane University*

HENRY BOYLAN ORTON, M.D., *Newark, N. J.*

WINFRED OVERHOLSER, M.D., *George Washington University*

FRANKLIN L. PAYNE, M.D., *University of Pennsylvania*

E. D. PLASS, M.D., *University of Iowa*

TRACY J. PUTNAM, *Beverly Hills, California*

B. O. RAULSTON, M.D., *University of Southern California*

LYMAN G. RICHARDS, M.D., *Massachusetts Institute of Technology*

HERMAN ROBBINS, M.D., *Hospital for Joint Diseases, New York, N. Y.*

RAYMOND R. SACKLER, M.D., *New York, N.Y.*

MILTON S. SACKS, M.D., *University of Maryland School of Medicine*

MAX S. SADOVE, M.D., *University of Illinois*

MORRIS SCHAEFFER, M.D., *Director, Communicable Disease Center, Montgomery, Ala.*

LEWIS C. SCHEFFEY, M.D., *Jefferson Medical College*

SIDNEY SCHERLIS, M.D., *Baltimore, Md.*

EDWARD A. SCHUMANN, M.D., *Phila., Pa.*

CYRUS C. STURGIS, M.D., *University of Michigan*

HERBERT THOMS, M.D., *Yale University*

DONALD V. TRUEBLOOD, M.D., *Seattle, Wash.*

JAMES J. WARING, M.D., *University of Colorado*

KARL M. WILSON, M.D., *University of Rochester*

FRED W. WITTICH, M.D., *Minneapolis, Minn.*

FLETCHER D. WOODWARD, M.D., *Charlottesville, Va.*

INTERNATIONAL EDITORIAL BOARD

ROMA AMYOT, M.D., *Editor-in-Chief, L'Union Médicale du Canada*

GASTON BACHELARD, M.D., *Directeur de l'Institut d'Histoire des Sciences, La Sorbonne, Paris, France*

GEOFFREY H. BATEMAN, *London, England*

PAUL DIEPGEN, M.D., *Director of Medizinhistorischen Institutes der Johannes Gutenberg Univ., Mainz, Germany*

PEDRO LAIN ENTRALGO, M.D., *Profesor de Historia de la Medicina, Madrid, Spain*

PROF. A. GIGON, *Schweizerische Akademie der Medizinischen, Wissenschaften, Basel, Switzerland*

EDV. GOTFREDSEN, M.D., *Director of the Universitetets Medicinsk-Historiske Museum, Copenhagen, Denmark*

DOUGLAS GUTHRIE, M.D., *Professor of the History of Medicine, University of Edinburgh, Edinburgh, Scotland*

WILLY HARTNER, M.D., *Johann Wolfgang Goethe Universität, Frankfurt a. M., Germany*

E. HINTZCHE, M.D., *Anatomisches Institut, Bern, Switzerland*

BJØRN IBSEN, M.D., *Chief of the Department of Anaesthesiology, Kommunehospitalet, Copenhagen, Denmark*

JUAN B. LASTRES, M.D., *Profesor de Historia de la Medicina, Universidad de San Marcos, Lima, Peru*

PROF. ADOLF MEYER-ABICH, *Elbchausee 460, Hamburg-Blankenese, Germany*

ANDRE MOULONGUET, M.D., *Paris, France*

PROF. RODOLFO PÉREZ DE LOS REYES, *Universidad de La Habana, Cuba*

AUGUSTO PI-SUÑER, M.D., *Instituto de Medicina Experimental, Caracas, Venezuela*

ILSE ROSENTHAL-SCHNEIDER, PH.D., *The University of Sydney, Sydney, Australia*

ANIBAL RUIZ MORENO, M.D., *Profesor de Historia de la Medicina, Buenos Aires, Argentina*

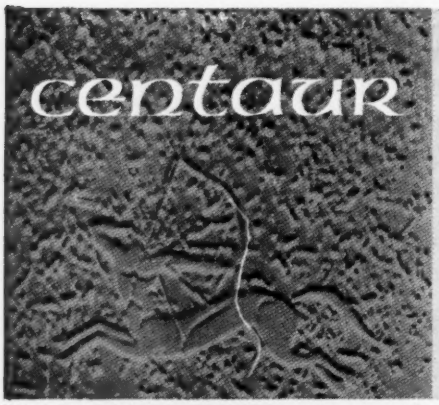
KENNETH F. RUSSELL, M.S., F.R.A.C.S., *Associate Professor of Anatomy, The University of Melbourne, Melbourne, Australia*

HANS SELYE, M.D., *Université de Montréal, Montreal, Canada*

PROF. IVOLINO DA VASCONCELLOS, *President, Sociedad Brasileña de Historia da Medicina, Rio de Janeiro, Brazil*

2 NEW BOOKS

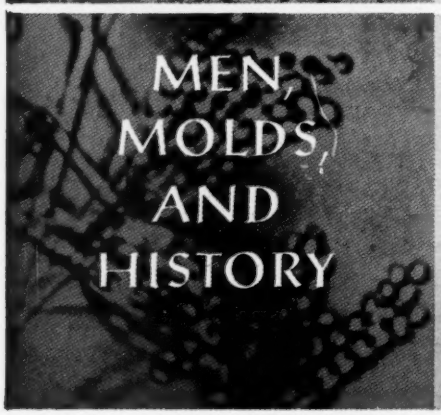
of outstanding medical distinction and significance



CENTAUR: Essays on the History of Medical Ideas
by Félix Martí-Ibáñez, M.D. **720 pages, $6**

The historical pageant of medicine
—in its full dimensions
—with its ultimate concept

The scope of this book is truly broad, not being limited by era or geography. Here are articles on the development of medicine in Don Quixote's Spain; William Harvey as a student in gay Padua; the influence of atomic science on modern art; the riddle of curare; the role of books and writing in the physician's life; the turbulent, bloody world of the artist-physician during the Renaissance; the psychology of Oriental rug symbols; the evolution of contemporary psychobiology; and many other notable and intriguing topics.



MEN, MOLDS, AND HISTORY
by Félix Martí-Ibáñez, M.D. **128 pages, $3**

The new world of antibiotics
—its over-all meaning in science
—its total impact on society

The history, present status, and probable future of antibiotics are presented with originality and profound insight, and their effects on science and civilization are shown with dramatic sweep. Among the subjects covered are: the search for the broad-spectrum antibiotics; important, related aspects of clinical medicine, general scientific research, medical education, and public health; the background of the clinical case history; words and medical communication; the relation of antibiotics to the art of translation; and others.

SPECIAL COMBINATION OFFER

MD PUBLICATIONS, INC.
30 East 60th Street, New York 22, N. Y.

Please send_____copies of Centaur: Essays on the History of Medical Ideas ($6)
and_____copies of Men, Molds, and History ($3)
— or send both books at the special combination offer of $8.

☐ *Bill me.* ☐ *Check enclosed.*

NAME

INSTITUTION

ADDRESS

CITY STATE

These two books, a panorama of the men, ideas, events, and places that made history, reflect the striking philosophical viewpoint of Félix Martí-Ibáñez, M.D. The author's colorful life enables him to think as a psychiatrist, historian, author, and soldier *malgré lui*. He has lived and extensively traveled in four continents, and has worked with dedication and achievement in the humanities and sciences, always maintaining his quest for the decisive messages of medical humanism and continuing his search for his own inner truth. At present, in addition to his writing and publishing, Dr. Martí-Ibáñez is Professor and Director of the Department of the History of Medicine, New York Medical College, and Editor-in-Chief of the medical newsmagazine, MD.

Beautifully designed in an unusual format and finely bound in durable cloth, both books are eminently readable and make a worthy addition to any library.

INTERNATIONAL RECORD OF MEDICINE

VOL. 173 NO. 6 WHOLE NUMBER 2928 JUNE 1960

H. Laborit, J. Drouet, J. Gerard, J. M. Jouany, C. Narvaes, P. Niaussat, and B. Weber — Odd Electron Structures in the Concept of "Metabolic Resuscitation": Therapeutic Introduction in Neuropharmacology and Psychopharmacology ... 351

R. A. Love — Personnel Decontamination Units at Brookhaven National Laboratory ... 365

David A. Hilding and John L. Fletcher — The Protective Value of the Middle Ear Reflex ... 369

William D. Gray — A Clinical Evaluation of Fluphenazine ... 375

Sidney Cohen — Notes on the Hallucinogenic State ... 380

Felix Marti-Ibañez — On an Armenian "Flying Carpet" ... 388

REVIEWS

J. Arthur Myers, editor — Diseases of the Chest including the Heart ... 390

William Harvey and the Circulation of the Blood ... 390

INTERNATIONAL CLINICAL NEWSLETTER ... 391

Forthcoming Symposium

A Symposium on the Mechanism and Management of Hemorrhagic Disorders in Children will be included in the July issue of *International Record of Medicine*. Included will be the following: Introduction, Biochemical Mechanism of Hemostasis, Diagnostic Procedures in Hemorrhagic Diseases of Children, Management of Hemorrhagic Diseases in Children, Disorders of the Hemostatic Mechanism, Thrombelastography in Hemorrhagic Disorders, The Management of Anticoagulant Therapy, Management of Blood Clotting Defects in Children, The Investigation and Treatment in Childhood of the Hereditary Hemorrhagic Disorders.

QUARTERLY REVIEW OF OPHTHALMOLOGY

HISTORICAL VIGNETTES

Three Physiologists: Their Impact on Ophthalmology: Young, Müller, and Helmholtz.... 395
GEORGE E. ARRINGTON, JR.

Preventive Ophthalmology.... 400
G. PETER HALBERG

OPHTHALMOLOGY ABSTRACTS

Ophthalmology Per Se

The Problem of Unilateral Amblyopia, an Editorial.... 402
The Diagnosis and Treatment of Simple Glaucoma.... 402
Surgical Rotation of the Eyeball.... 402
Studies on the Living Cornea in Vitro. 1. Methods and Physiological Measurement.. 403
Studies on the Living Cornea in Vitro. 2. The Active Transport of Sodium Across the Epithelium.... 403
Studies on Intraocular Effects of the Orbital Parasympathetic Pathway. III. Effect of Steady State Dynamics.... 404
Congenital Dyslexia: A Problem in Etiology.... 404
Degeneratio Punctata Albescens.... 404
Conjunctival Amyloidosis.... 405
Some Observations in Entropion and Ectropion and a Method of Conjunctivo/rhinostomy.... 405

Medical Ophthalmology

Evaluation of Ocular Signs and Symptoms in Myasthenia Gravis.... 405
Neuro-ophthalmologic Evaluation of Abducens Nerve Paralysis.... 406
Ocular Complications in Sickle-Cell Hemoglobin C Disease.... 406
The Pathology of Mikulicz-Sjogren Disease in Relation to Disseminated Lupus Erythematosus. A Review of the Autopsy Findings and Presentation of a Case.... 407
Local Administration of Anticholinesterase Agents in Ocular Myasthenia Gravis.... 407
Emotional Glaucoma.... 407
Experimental Diabetic Retinopathy.... 407
Ocular Findings in Cystic Fibrosis of the Pancreas.... 408
The Probable Role of Benign Histoplasmosis in the Etiology of Granulomatous Uveitis. 408

QUESTIONS AND ANSWERS.... 409
DAHAR CURY

INTERNATIONAL RECORD OF MEDICINE

VOL. 173 NO. 6 WHOLE NUMBER 2928 JUNE 1960

Odd Electron Structures in the Concept of "Metabolic Resuscitation"

Therapeutic Introduction in Neuropharmacology and Psychopharmacology

H. Laborit, J. Drouet, J. Gerard, J. M. Jouany, C. Narvaes, P. Niaussat, and B. Weber

SECTION DE RECHERCHES PHYSIOLOGIQUES DE LA MARINE NATIONALE, LABORATOIRE D'EUTONOLOGIE, HÔPITAL BOUCICAUT PARIS, FRANCE

The protecting action of serotonin against convulsions induced by oxygen under pressure in mice was demonstrated for the first time in 1957 by one of us, in collaboration with Broussolle and Perrimond-Trouchet at the Groupe d'Etudes et de Recherches Sous-Marines at Toulon.[1] Shortly thereafter, we showed that serotonin possessed plant growth–promoting properties similar to those of the auxins.[2] More recently, we attributed the origin of these two activities and the action of serotonin on the nervous system to its antioxidant properties.[3] We have concurrently studied other antioxidants, and we recently published a pharmacological study on the peripheral activity of 2-aminoethylisothiouronium.[4] Early in our investigations, we were struck by the fact that a large number of these antioxidants possess an identical action on nerve centers, although they belong to chemically different groups. In addition to antagonizing postelectroshock coma, many of these agents produced remarkable recovery after severe experimental cerebral anoxia performed without physical or pharmacological protection. The agents also caused a state of neuromuscular excitation of a special type, which was regarded as a specific syndrome. The first results obtained in the treatment of the comatose state in man, follow the same pattern. Our experimental results will be mentioned elsewhere, and we can only summarize them here.

Certain leading concepts are relevant and will be reviewed schematically. We have made an integration of these concepts, which may appear somewhat premature, but does have the advantage of setting forth a number of experimental observations that we consider important.

THE ANTIOXIDANT CONCEPT

The oxygen atom has six electrons on its peripheral orbit. Two of these spin in the same direction and consequently are not "paired." The oxygen molecule (O_2) thus still has two unpaired electrons; it is a double free radical. A free radical is an atom or a molecule that has on its peripheral orbit (the active orbit in biological chemistry and the one that reacts with the elements or molecules in its vicinity) an unpaired electron or even two, as is the case with atomic and molecular oxygen. These atoms or molecules, which possess an odd number of electrons, are necessarily paramagnetic and consequently very reactive. They tend to pair up their odd electrons, and therefore they are capable of creating in their vicinity new molecules having an odd number of electrons, i.e., new free radicals, and thus of originating a chain reaction that may disrupt the organization of living matter.

Ionizing radiations act through the formation of free radicals, and the energy they contain is capable of exciting molecules, i.e., of causing one of their electrons to jump from a deeper orbit into a more peripheral one. This electron then becomes unpaired in this orbit, and if it reaches the most peripheral orbit, it may give rise, under certain conditions, to a free radical. The role of an antioxidant will be, in the case of oxygen, for instance, to pair up its unpaired electron to give rise to a stable molecule and thus to deprive the oxygen of the "toxicity" resulting from its free radical nature. It is therefore understandable that the majority of antioxidants, which have a protective action against ionizing radiations, also have a protective action against the toxicity of oxygen under pressure. Their molecule contains labile hydrogen atoms, which, by splitting off, leave behind a free radical. This latter can combine preferentially with oxygen or with another free radical and thus give rise to a stable molecule. The chain reaction is then stopped, and this mechanism distinguishes antioxidants from ordinary reducing compounds.

ENZYME REACTIONS

At this point, we wish to link the preceding concept with a short discussion on enzyme reaction kinetics. The utilization of the energy contained in substrates by the living cell is possible only because of the presence of an electron transport mechanism, which is characteristic of the cell oxidation-reduction processes. Most of the substrates or products resulting from the oxidation-reduction processes are molecules in which electrons are paired. It could be then conceived that electrons are transferred in pairs, but the required activation energy would be very high, and moreover, it is known that certain electron transport systems, such as the cytochromes, require organometallic molecules, which can perform the transfer of only one electron.

Consequently, Michaelis[18] has suggested the hypothesis that the oxidation of organic molecules (i.e., most frequently their dehydrogenation and the removal of electrons) takes place by successive steps involving only one electron. As a result, it can be seen that the intermediate molecule is a free radical. These concepts imply that in the majority of enzyme reactions, the enzyme plays an active part as an electron carrier, thus facilitating the formation of a free radical, which is the inter-

mediate structure between the electron donor and the acceptor. This would seem to support certain recent methods of investigation that call on the spectrophotometric absorption associated with electron spin resonance.

Another concept that could be integrated here is the "continuum" concept suggested by Szent-Gyorgyi. Also, Szent-Gyorgyi has stressed the essential difference that exists between extracellular and intracellular water. In his opinion, extracellular water is dipolar and, therefore, necessarily "ionizing." It facilitates the rupture of bonds through heterolysis. Intracellular water, on the contrary, possesses a crystalline structure and thus protects the excitation state of molecules from the kinetic energy of thermal collisions and facilitates the splitting of these molecules through homolysis. In this case each fragment preserves an unpaired electron on the atom that was previously bound and is a free radical.[5]

COENZYME Q AND THE CONCEPT OF COUPLING BETWEEN PHOSPHORYLATION AND OXIDATION

The stripping of electrons from the substrate and their transfer all the way to oxygen during energy-liberating oxidative phenomena has been mentioned. This energy can be temporarily stored in high-energy phosphate bonds or immediately freed as heat. The storage is restricted to one bond for each step of electron transfer. Since the transfer of an electron pair from the substrate to the oxygen can liberate a large amount of energy, it is beneficial for this transfer to take place in multiple and successive steps. Some of these steps will permit the formation of a high-energy phosphate bond due to a mechanism that couples phosphorylation and oxidation so that a very large share of the energy liberated from the substrate is stored and very little lost as heat. The levels at which coupling takes place along the respiratory chain are probably the following:

$$\begin{array}{l} \qquad\qquad\quad \text{ATP} \qquad\qquad\qquad\qquad\quad \text{ATP} \\ \qquad\qquad\quad \nearrow \qquad\qquad\qquad\qquad\quad \nearrow \\ \text{Substrates} \rightarrow \text{DPN} \rightarrow \text{Flavoproteins} \rightarrow \text{Cytochrome b} \rightarrow \text{Cytochrome c} \rightarrow \\ \qquad\qquad\quad \text{ATP} \\ \qquad\qquad\quad \nearrow \\ \text{Cytochrome a} \rightarrow \text{Chytochrome a3} \rightarrow O_2. \end{array}$$

This coupling takes place in lipoprotein-rich mitrochondria. Some of these lipoproteins seem to be situated between certain elements of the respiratory chain of electron transport in such a way that any one element of this chain reacts with the next one only through the interplay of the lipoprotein fraction. A coenzyme has been discovered in this fraction, which, because of its quinone structure, has been named coenzyme Q. Green[6] has suggested that it participates not only in electron transport, but also in the concomitant phosphorylation. According to him, coenzyme Q would accept one electron from a substrate and thus would be reduced to give a semiquinone, which then would react with inorganic phosphate as shown in figure 1. Now semiquinones are regarded as typical antioxidants.

We have used hydroquinone experimentally. It undergoes auto-oxidation to yield either one of two semiquinone structures, giving rise through resonance to a structure intermediate between semiquinone and quinone[8] (fig. 2).

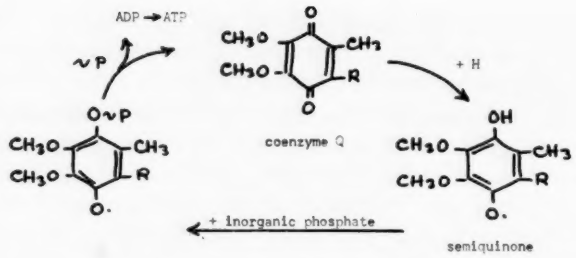


FIG. 1. Coenzyme Q accepts one electron from a substrate and thus is reduced to give a semiquinone, which then reacts with inorganic phosphate.

As far as phenothiazine is concerned, its antioxidant property is probably related to the formation of semiquinone type radicals (fig. 3). In figure 3, either structure E or F could combine with molecular oxygen as well as with free radicals. In chlorpromazine, however, the dimethylaminopropyl chain is connected with the nitrogen atom. Now, Szent-Gyorgyi[7] has demonstrated that chlorpromazine is capable of depressing the excited state of certain molecules by bringing back an unpaired electron from a peripheral orbit toward a more central one. Chlorpromazine presents opposite properties to those that we have demonstrated in antioxidants.

The antioxidant property of tocopherols (vitamin E = α tocopherol) is again due to the formation of semiquinone structures.[8]

These observations deserve a longer discussion, but we have mentioned them here only as an introduction to the hypothesis that has guided this work: *The concept of the single electron transfer that seems typical of intracellular phenomena and enzyme reaction could offer a new and fruitful approach to pharmacology.*

To test this hypothesis, studies were made with some antioxidants. *It would be expected that these antioxidants would act not so much on molecular oxygen, but rather interfere within enzyme reactions by acting on the free radicals to which they give rise.*

CHEMICAL GROUPS STUDIED

As a support to our hypothesis, we were able to observe that very different com-

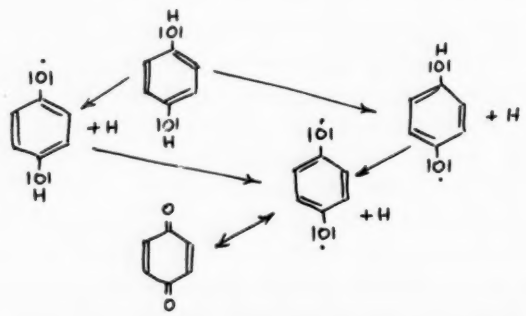


FIG. 2. Hydroquinone undergoes auto-oxidation to yield either one of two semiquinone structures, giving rise through resonance to a structure intermediate between semiquinone and quinone.

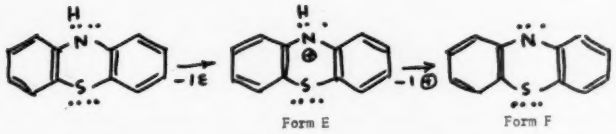


FIG. 3. In the case of phenothiazine, the antioxidant property is probably related to the formation of semiquinone type radicals.

pounds possessing only antioxidant properties in common caused the same neurological syndrome (fig. 4).

Many growth hormones and their derivatives, as well as certain compounds containing an indole nucleus, can probably be included among this group of substances.

Some of the compounds studied potentiate each other's action on blood pressure. For example, a considerable hypertensive action is observed when certain compounds, which are slightly or not at all hypertensive themselves, are combined, such as 2-aminoethylisothiouronium and ascorbic acid, or 30 per cent hypertonic glucose.

Theoretically, hydroxyl, amino, and sulfhydryl groups alone or combined in specific positions, or associated with certain substituents, should be effective.[9]

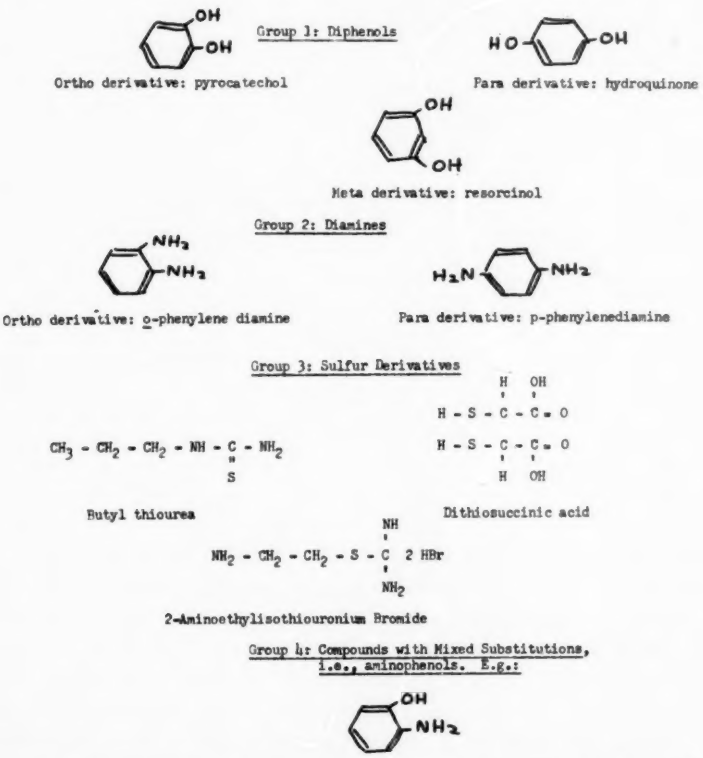


FIG. 4. Four groups of compounds with only antioxidant properties in common that caused the same neurological syndrome.

It should be stressed, finally, that the physiobiological properties that have been considered and that are described here have been limited by the simple techniques used. These are based on the effects of the drug: on the recovery of the functions of the central nervous system after anoxia, on conventional pharmacological methods, on duplication of the neuromuscular syndrome, on electroshock and pentylenetetrazol convulsion, and when applied directly to the cortex. Some compounds that are considered to have antioxidant properties are, nevertheless, inactive in these tests and can even have an opposite action. This may be due to their particular oxidation-reduction potential since a given potential is probably required for the effectiveness of the compound on certain cell structures.

We shall mainly consider here the central action of these compounds, and we feel that certain of its aspects can be accepted now. But first, it is necessary to describe a few other concepts that we have tried to integrate, dealing with the nature of synaptic transmission.

THE NATURE OF SYNAPTIC TRANSMISSION

Conduction electrogenesis and synaptic electrogenesis should not be mistaken for one another.

Conduction electrogenesis is stimulated by electrical depolarization and potassium ion. It is always depolarizing, it responds generally to the all or none law, and it is blocked by hyperpolarization. Synaptic electrogenesis, on the contrary, is insensitive to electrical stimuli and to potassium ion, can be hyperpolarizing or depolarizing, is gradated and reversible, and response can take place during the hyperpolarization phase.

In contrast to conduction electrogenesis, synaptic electrogenesis is, moreover, very sensitive to drugs.

As a result of these characteristics, synaptic transmission can hardly be explained by an electrical phenomenon that appears to be, when it takes place, only of secondary importance.

Grundfest[10] observed that the same neuron must possess both an electrically excitable and a chemically excitable membrane (the receptor). The latter must work together with the former and stimulates or inhibits it. Finally, if electrogenesis takes place at the extremity of the neuron, it must be accompanied there by the secretion of a chemical mediator.

Acetylcholine is the best and longest known chemical mediator of the nervous influx transmission. Its synthesis requires the presence of coenzyme A and an energy source, adenosine triphosphate, which implies its close dependence on oxidative processes. Certain observations have led to the belief that dimethylaminoethanol rather than choline is the intracellular precursor of acetylcholine in man.

Moreover, the investigations of Koshtoyants and Babskaya[11] have demonstrated that the activity of acetylcholine at the level of synapses results from its combination with the S-H groups of proteins. We must also remember the part played by coenzyme A-SH in the acetylation of choline. Tarakhovskii[12] recently reported that ganglionic blockers of the hexamethonium type act by competing with acetyl-

choline for the S-H groups of protein and that their action on the isolated heart can be prevented by the use of cysteine, reduced glutathione, or urea. The first two compounds are antioxidants with a low potential, whereas the latter frees the reactive sulfhydryl groups of proteins. Finally, we discovered that 2-aminoethylisothiouronium (which also liberates S-H groups) antagonized the action of ganglionic-blocking agents. Thus certain antioxidants, at least those that we have studied, seem to protect the synthesis of acetylcholine, and this is interpreted as being due to the protection of the oxidative processes associated with phosphorylation.

Moreover, for some time there has been a tendency to attach more importance to the role of γ-amino-butyric acid in inhibition phenomena. γ-Amino-butyric acid derives from α-ketoglutaric acid through glutamic acid. Now, in the Krebs cycle, the rate-determining reaction is the conversion of α-ketoglutaric acid into succinic acid. Regardless of the degree of stimulation of the preceding metabolic steps, the rate of this reaction does not vary, and if it cannot cope with an increase in rate of the previous steps, α-ketoglutaric acid will accumulate and give rise to glutamic acid and then to γ-amino-butyric acid. In our opinion, it can be concluded therefrom that any stimulation of the oxidative cycles beyond a certain intensity will lead to an increased production of γ-amino-butyric acid and to an inhibition of the depolarizing synapses.

There is another factor, however, worth mentioning: The rate-determining reaction between α-ketoglutaric and succinic acid is catalyzed by coenzyme A and diphosphopyridine nucleotide. We feel that it is at this level that the main action of antioxidants could take place. They would speed up this so-called rate-determining step of the oxidative cycle.

STUDY OF THE MECHANISM OF ACTION OF NARCOTICS

Study of the mechanism of action of narcotics has enabled us to define some of the relationships that exist between respiratory phenomena in neurons and the functional activity of the brain. Narcotics are inhibitors of cerebral oxidative phenomena. Brain tissue slices, using glucose as substrate, show an increase in the intensity of these oxidative processes when the potassium ion concentration of the solution in which they are bathed is increased. Narcotics inhibit this potassium ion effect. A nerve at rest elicits metabolic processes that are not sensitive either to narcotics or to potassium. On the contrary, this phase, which we shall call "potassium sensitive," becomes predominant in the stimulated nerve.[13] Attention is drawn to the association of these observations with the preceding ones concerning the distinction between synaptic and conducting membranes.

The synthesis of adenosine triphosphate is necessary for oxidative processes just as much as the latter are necessary for the synthesis of adenosine triphosphate and for the maintenance of nerve functions. As previously mentioned, adenosine triphosphate is also necessary for the synthesis of acetylcholine. Narcotics inhibit the synthesis of acetylcholine by blocking the formation of adenosine triphosphate through the inhibition of coenzyme A.[13]

Here again we find the concept of coupling between phosphorylations and oxida-

tions. Narcotics "uncouple" mainly by preventing phosphorylations. We shall add that since these phosphorylations are necessary for the utilization of substrates and for their oxidation, this oxidation should be secondarily slowed down, and this is what is actually observed experimentally.

Moreover, since oxidative processes control the intracellular ion concentration, the polarization of the electrically excitable membrane, and the cell autoregulation, it is conceivable that a disturbance of these processes leads to the stable depolarization and to the functional inhibition of the cell.

Thus regardless of the aspect considered—metabolic or electrogenetic—the distinction must always be made between phenomena caused by electrical stimulation, or potassium, and synaptic phenomena. The phenomena caused by electrical stimulation (potassium sensitive) are directly inhibited by narcotics. The synaptic phenomena are inhibited indirectly through the lack of acetylcholine synthesis. The uncoupling between phosphorylation and oxidation caused by narcotics is at the origin of these inhibitory mechanisms.

SCHEMATIC REPRESENTATION AND DISCUSSION OF EXPERIMENTAL RESULTS OBTAINED WITH SOME ANTIOXIDANTS

The study of some antioxidants has yielded experimental observations too numerous to be reviewed fully here. The peripheral pharmacological actions are rather similar but for small variations, and it is this action that we have described in our study of 2-aminoethylisothiouronium,[4] to which the reader should refer. One fact stands out: the difficulty of integrating the action of these agents within the general framework of conventional pharmacology. Their action, which is as much peripheral as central, requires that *they be regarded as drugs playing a part in an essential metabolic process* not located on the surface of the membrane where oxygen acts, but that is concerned with the activity of enzyme reactions.

Our experimental observations with some antioxidants can be summarized as follows:

In the Animal. Parenteral administration of average doses did not alter the behavior of the animals. Large parenteral doses of all the compounds previously listed caused an identical syndrome characterized by the appearance within two to three minutes of tremulations and uncoordinated muscular jerks associated with a decrease in muscle tone. The animal was spread out in a typical position with the posterior limbs in extension. As early as 1936, Bacq[14, 15] had observed that catechol caused generalized tremors. We also observed this phenomenon with all the drugs we studied. There have never been either convulsions or rigidity or loss of consciousness. The return to normal after 20 to 40 minutes, depending on the dose used, was sudden and without sequelae. Thereafter, the same syndrome could be repeated with a new injection. The injection of a massive dose of gallamine triethiodide, under controlled ventilation, suppressed the uncoordinated movements.

This neuromuscular syndrome is not prevented in the rat by scopolamine, atropine, diethazine, Hydergine, or Hemineurine, or by thiopental sodium, which causes hypnosis without suppressing the syndrome. It is prevented only by chlorpromazine

in a 2 mg./Kg. dose injected 20 minutes before, but when it is injected simultaneously or later, it is ineffective. Electroshock also prevents this "excitation-hypotonia" syndrome. Calcium chloride, an uncoupling agent, retards its appearance considerably (10 minutes).

The direct application of one of these agents to the cortex of the conscious animal caused convulsions but these were without a tonic phase and without contracture. If the cortical application was performed after the application of traces of epinephrine, the reaction was amplified. It was inhibited by local application or intravenous injection of chlorpromazine. Local cortical application caused a peripheral hypertension and potentiated the hypertension resulting from the application of traces of epinephrine to the same area.

In cerebral anoxia in the rabbit produced by circulatory arrest for 17 to 25 minutes according to the technique that we described previously,[16] the following effects were observed: absence of definite protection of cerebral anatomy by prophylactic use of these drugs and a spectacular recovery of cerebral functions by curative use (a few hours later the animals showed normal behavior and they moved spontaneously).

Experimental electroshock in the rat seems to be the most efficient method of central depolarization. After the injection of antioxidants (diphenols in particular), convulsions were identical to those of the control group but were not followed by a coma; the duration of action of the tremulation syndrome caused by quinones was markedly shortened and the decrease in muscle tone was much smaller. If the injection was given immediately after the electroshock at the onset of coma, the latter ended as soon as the drug began to act (two minutes), *but the tremulations caused by quinones did not appear.* Similarly, the mortality from pentylenetetrazol convulsions was markedly decreased.

Certain differences were noted in the action of these drugs.

Diphenols were easier to handle and not very toxic. Neuromuscular effects were immediate, lasted 30 minutes for one dose, and varied according to the drug used. Resorcinol was much less powerful. It behaved much like the previous agents, although certain objections could be made on theoretical grounds.

Diamines had a slower onset of action but their action lasted from one to many hours. Even after disappearance of the syndrome, the animals remained hyperexcitable. Diamines, moreover, were more toxic.

Thiols also had a slow onset and a short duration of action, and effective doses were almost toxic. Only 2-aminoethylisothiouronium, with which we are quite familiar experimentally and clinically, had a low toxicity. A dose of 300 to 500 mg. could be injected intravenously in a glucose solution safely in man over 30 minutes.

Aminophenols had an action similar to that of diphenols.

In any event, we are not ready yet to choose from the large number of antioxidants those that may have the greatest potential in human therapy. Many years of work will be required to determine this.

In Man. Although our experience in man is still limited, some patients, who had been in coma for many weeks, regained consciousness after two to three days' administration of some of these drugs.

DISCUSSION

The antioxidants studied seem to possess little prophylactic activity against stress or aggression; *they appear, however, to be capable of reactivating certain inhibited enzyme systems*. A tentative explanation of the mechanism of action of the antioxidants can be based on the following observations:

At the Cellular Level.

In Anoxia. The absence of oxygen—the electron acceptor at the surface of the cell—produces an electron "accumulation" manifested in this case by the well-known lowering of the intracellular rH_2. It is suggested that after anoxia, antioxidants would act by liberating their labile hydrogen atoms and would be capable of starting again the oxidative processes coupled with phosphorylations. One consequence would be return of the ability of the neuron to synthesize acetylcholine and perhaps sparing or reactivation of epinephrine.

In the Normal Animal. Studies were made after parenteral administration or cortical application.

Experimental results cannot be regarded as the consequence of cerebral anoxic or histotoxic phenomena, at least for average doses, because: (a) They are not accompanied either by convulsions or rigidity, and they are rapidly reversible and without sequelae. (b) When the brain has suffered anoxic anoxia sufficient to cause irreversible lesions, the functional recovery is exceptionally rapid and is not compatible with a toxic action. (c) In the dog under controlled ventilation, deep hypothermia between 10 and 15 C. can be obtained with maintenance of effective cardiovascular functions (arterial blood pressure between 50 and 100 mm. of mercury). Thus we were able to perform vascular and simple nervous system resuscitations after circulatory arrest of more than 1½ hours without resorting to extracorporeal blood circulation. This again raises the question of the metabolic orientation of hypothyroid hibernating animals. (d) It is suggested that the neurological behavior of the animal treated with antioxidants after electroshock (depolarization) furnishes proof that these compounds facilitate repolarization, i.e., cause a considerable improvement of recoupling processes, since a true antagonism seems to exist between the effects of the electrical phenomenon and of the chemical phenomenon.

These observations cannot be explained by a disturbance of oxidative cycles leading to an uncoupling in the usual sense of the word. On the contrary, although the compounds studied do not possess a definite anticholine-esterase action, the vasodilation, bradycardia, and occasional salivation observed can be attributed to an increase in acetylcholine synthesis. The absence of an increase in oxygen consumption can be attributed to a relative facilitation of phosphorylations over oxidations. The deep and spontaneous hypothermia with high doses also supports this view, as does the antithyroid activity demonstrated in thyrotoxic patients receiving 2-aminoethylisothiouronium. It is known that thyroxin uncouples phosphorylations from oxidations. So does chlorpromazine, and so far it has been the only drug we have found capable of antagonizing the action of antioxidants. The frequent potentiation of the hypertension caused by atropine probably indicates a certain amount of synaptic ganglia stimulation. The delaying action of Ca^{++} (an uncoupling agent) on the quinone-induced syndrome can be similarly explained.

The adrenolytic action of chlorpromazine is well known and the action of antioxidants, when applied locally to the cortex, has been mentioned. A peripheral protecting action on epinephrine appears to exist and could be due to an extracellular antioxidant action. If the observations made during the general pharmacological study (prolongation of the hypertensive effect of epinephrine injected intravenously) are taken into account, they suggest that the action of these drugs, whether peripheral or central, is dual and balanced, cholinergic and adrenergic. This probably explains the minor effect of the agents studied on blood pressure in the dog and in man, the nearly constant hypotensive action in the rabbit, as well as the peripheral actions, which combine the effects of cholinergic and of adrenergic drugs. The mechanism of their action toward epinephrine, itself an orthoquinone, however, is less easily explained. Axelrod[17] and some other investigators have suggested that epinephrine is deactivated by the enzyme O-methyltransferase. It might be that the agents studied inhibit this enzyme.

A suggested explanation for all the phenomena follows.

Some antioxidants would act by facilitating the action of diphosphopyridine nucleotide, of coenzyme A, or of coenzyme Q in the reactions in which they are involved. They could either reactivate or play an intermediary part in these reactions. One of these reactions, especially that between α-ketoglutaric and succinic acids, controls the rate of the tricarboxylic acid cycle. The speeding up of this reaction should permit a speeding up of the whole cycle, and the shunt mechanism leading through glutamic acid to the formation of γ-amino-butyric acid, a central inhibitor, would now be more active. Thus, at the central biochemical level, a metabolic stimulation that preserves coupling phenomena would be associated with an increased inhibition. At the neurophysiological level, the result would be an increase in the acetylcholine synthesis and an over-all stimulation of the facilitating and inhibiting synapses.

This latter stimulation, however, would not lead to stable depolarizations, as it would with drugs depressing adenosine triphosphate stores, unless large dosages of the antioxidants were used. The stimulation would also be different from that caused by cholinergic drugs because it is the consequence and not the cause of an activation of metabolic processes, possibly also because it takes place harmoniously by coupling phosphorylation and oxidations. The behavior of the animal under the action of these drugs, after both anoxia and electroshock, seems to support this hypothesis.

On the Neurophysiological Level. It is too early to attempt to define the existence of a more or less specific action on a particular system without a specific study. Certain observations, however, should be kept in mind:

The appearance of the animal should not be overlooked. It shows: generalization of tremulations, hence a considerable activation of the medullary motor neurons; a decrease in tone, hence a stimulation of the inhibiting corticomedullar pathways that go through the red nucleus; a predominance of extension, hence a stimulation of the vestibulospinal pathways; by the inhibitory action of chlorpromazine, on the one hand, and the absence of action of thiopental sodium and of Hemineurine, on the other, a stimulating action on the ascending activating and on the descending facili-

tating reticular formations. This is not illogical if it is admitted that these "recoupling" agents facilitate the synthesis of acetylcholine and protect epinephrine from oxidation. An action on the cortical inhibiting zones or on the inhibiting descending reticular formation is not excluded either, since, if our hypothesis is correct on the metabolic level, we would be dealing with an action on a fundamental process with consequently extremely wide functional repercussions. Thus it appears that the tremulating agitation combined with the decrease in tone could be accounted for by a generalized synaptic stimulation, which converges toward the common final pathway. But attention must be drawn to the benign nature of such a condition and its favorable action after anoxia, which seems to show that no stable disturbance of metabolic processes takes place with therapeutic doses.

We are thus tempted to call these agents "recoupling agents," whereas until now, general pharmacology and biology have used mainly "uncoupling agents," such as general anesthetics and thyroxin, not to mention epinephrine, bishydroxycoumarin, chlorpromazine, etc. Also, some of the latter agents seem to facilitate oxidation (thyroxin, epinephrine), others to inhibit preferentially phosphorylation without stimulating oxidation, if only for a short period at the beginning of their action (general anesthetics, phenothiazines). The antioxidants that we have studied thus appear to us as "metabolic resuscitators" in clinical doses, which, of course, are smaller than those capable of producing the syndrome described previously.

The suggested interpretation of the mechanism of action of some antioxidants may provide neuropharmacology and psychopharmacology with a new approach to improving their therapeutic armamentarium. Synaptic stimulation or inhibition, conduction stimulation or inhibition are all directly related to metabolic disturbances, as are probably various psychopathic and neurological states.

This paper has been intentionally limited to a superficial review of the metabolism of the neuron. We shall report detailed experimental studies and first clinical results elsewhere. These observations may have an effect on the entire study of physiopathology if efforts are directed toward the calculated orientation of various metabolisms in a selected direction and for a particular aim. It is obviously difficult now to predict all the therapeutic orientations to which such a concept may lead, if proved right. In the field of neuropsychiatry, as well as traumatic, toxic, metabolic, post-insulin shock, and postelectroshock comas, certain syndromes, such as schizophrenia, merit study. It is, moreover, difficult to predict a priori which psychoses are most likely to benefit from these findings.

It also seems worth while to study these agents in all the peripheral metabolic disturbances and, in particular, in various endocrine syndromes (of pituitary and thyroid origin) and in syndromes of pancreatic and adrenal origin. The problems of fatigue and of aging should be approached similarly.

Severe stress-induced postaggression lesion syndromes and cardiac pathologies (atherosclerosis, fat metabolism disturbances) should also be studied. Finally, the action of these agents might also be studied in the evolution of certain cellular disturbances, the origins of which appear to be chaotic disturbances in the electron transfer mechanism at the molecular level. *Thus certain antioxidants, probably recoupling agents, appear to open new therapeutic possibilities, not so much by creating new*

functional conditions with additional metabolic disturbances, as by "resuscitating" certain disturbed essential metabolic processes.

We have always advocated rest, whether at the molecular, cellular, or organic level, as a protection against stress, and now we must also consider the possibility of reactivating enzymatic lesions when they are still reversible. In addition to pre-, per-, and poststress therapy of the reaction syndrome, the possibility of some form of therapy aimed at correcting biochemical lesions can be conceived.

SUMMARY

The authors have demonstrated the similar physiological properties shared by certain compounds belonging to different chemical groups, but all capable of giving rise to structures containing odd electrons (diphenols, aminophenols, diamines, sulfur derivatives).

These properties are characterized by: a similar neurological syndrome "of excitation hypotonia," the suppression of postelectroshock coma, a decrease of the intensity of pentylenetetrazol convulsions and of their mortality, and rapid recovery of the central nervous system after anoxia. In man, some instances of return to consciousness after prolonged coma have also been noted.

The authors discovered these properties while studying so-called antioxidants, among which they also classify certain compounds containing an indol nucleus and certain plant growth hormones. These compounds possess labile hydrogen atoms and are capable of giving rise to free radicals; some of these could play a part in enzyme reactions (involving one electron transfer mechanisms), either by reactivating them or by playing the part of an intermediate in their mechanism. Certain observations suggest that these agents facilitate coupling between oxidations and phosphorylations and the synthesis of acetylcholine. Others, however, suggest that they also protect epinephrine from inactivation.

In any event, many of these compounds give rise to semiquinoid structures (odd electron structures), and the authors stress the possible importance of coenzyme Q, which also gives rise to a semiquinone, in the combined processes of oxidation and phosphorylation.

After integrating some recent concepts concerning the mechanism of synaptic transmission and of the action of narcotics on metabolism, and after reporting on use of those compounds generally regarded as "toxic", the authors attempt to interpret the observed experimental facts as much on the metabolic as on the neurophysiological plane.

It would seem likely that these concepts and the first experimental results reported lead the way, as much in neuropharmacology and psychopharmacology as in general physiopathology, to a true "metabolic resuscitation." The authors also suggest a few of the possible clinical applications.

BIBLIOGRAPHY

1. Laborit, H.; Broussolle, B., and Perrimond-Trouchet, R.: Compt. rend. Soc. de biol. *151*:930–933, 1957.
2. Niaussat, P.; Laborit, H.; Niaussat, M., and Dubois, C.: Compt. rend. Soc. de biol. *152*:945–947, 1958.

3. Laborit, H.; Niaussat, P.; Broussolle, B., and Jouany, J. N.: Presse méd. 23:927–947, 1959.
4. Laborit, H.; Broussolle, B.; Jouany, J. M.; Niaussat, P.; Reynier, M., and Weber, B.: Thérapie *14*:1116–1135, 1959.
5. Szent-Gyorgyi, A.: Muscular Contraction, New York, Academic Press, Inc., 1951, ed. 2.
6. Green, D. E.: Mechanism of Biological Oxidation, Cambridge, 1940.
7. Szent-Gyorgyi, A.: Science *124*:873–875, 1956.
8. Michaelis, L., and Wollman: Science *109*:313, 1949.
9. Vigneron, M.: Autooxydation, mesures de prévention. Antioxydants, Paris, Société d'éditions Pharm. et Scientifiques, 1 vol., 1956.
10. Grundfest, H.: Fed. Proc. *17*:1006–1018, 1958.
11. Koshtoyants, Kh. S., and Babskaya, N. E.: Acad. des sciences méd. de l'U.R.S.S. *47*:39–42, 1959.
12. Tarakhovskii, M. L.: Acad. des sciences méd. de l'U.R.S.S. *47*:83–87, 1959.
13. Quastel, J.: Report to the Second International Congress of Biochemistry, Brussels, 1955.
14. Bacq, Z. M.: Arch. internat. de physiol. *42*:340, 1936.
15. Bacq, Z. M.: Arch. internat. de physiol. *44*:15, 1936.
16. Niaussat, P.; Laborit, H.; Weber, B.; Baron, C., and Broussolle, B.: Presse méd. *42*:1578–1581, 1959.
17. Axelrod, J.: Science *126*:400, 1957.
18. Michaelis, L.: *In:* Summer, J. B., and Myrbäck, K., editors: The Enzymes, New York, Academic Press, Inc., 1951, vol. 2, part 1, chap. 44.

REVISTA DE PSICOLOGIA GENERAL Y APLICADA

Experimental and General Psychology, Applied Psychology, Pedagogy, Industrial, Economic, and Social Sciences

Director: José Germain

Scientific Counsel: Gregorio Marañón, Juan Zaragüeta, Manuel Soto
Managing Editors: José M. Sacristán, Ricardo Ibarrola

In its pages the reader will find articles of great scientific value, commentaries of special interest on current events in the psychologic field, books, tests and experimental apparatus, and vast and select bibliographic and clinical information.

Quarterly publication, 800 pages each year. Subscription rates: U. S. $2.00 for Spain and America; U. S. $2.50 for foreign subscriptions; U. S. $.60 for single issues.

Plaza de Santa Barbara, 10, Madrid, Spain

Personnel Decontamination Units at Brookhaven National Laboratory

R. A. Love, M.D.

MEDICAL DEPARTMENT, BROOKHAVEN NATIONAL LABORATORY

UPTON, LONG ISLAND, N. Y.

At an installation operating large nuclear reactors, such as Brookhaven National Laboratory, where there is a potential danger of contamination of many persons with radioactive materials, it is essential to have the means of coping with a major radioactive contaminating accident. As part of the method of meeting such a problem, if it should arise, a decontamination suite was incorporated in the construction of our new medical research center. It is located at the far end of the clinic wing with a separate entrance so that contaminated persons do not enter through the regular clinic door. This reduces the chance of spreading contamination to the clinic proper or the hospital where such contamination might severely limit or prohibit normal operations. The purpose is to reduce contamination capable of being spread to inconsequential or manageable quantities, so that necessary medical and internal decontamination procedures will not be hampered.

The suite consists of two identical units plus a separate shower for use by personnel who may need to wash after caring for contaminated patients. The duplication permits the women to use one unit while the men use the other or alternatively provides twice the capacity. If only a few women and a large number of men are involved, as soon as the women have been processed, both units become available for decontamination of the men. Access to each unit is directly from the outside into a room in which the fixed equipment consists of two showers, a sink, and a toilet. The walls of the room are covered with an impervious plastic coating to prevent contaminating materials from soaking in and to facilitate cleaning if contamination of the walls occurs.

Rather than separate shower stalls, the shower area is completely open without a partition between the two shower heads, which project out from opposite walls seven feet apart at such an angle that the sprays, which can be varied in strength and size of the streams, overlap at the level of a patient on a litter. This makes it possible to roll a seriously injured or unconscious patient on a litter under the shower heads where he can receive surface decontamination. A Stokes stretcher is quite suitable.

Under ordinary circumstances the waste water from the showers flows directly into the main sewer system. If the anticipated radiation level of the waste water is high, the flow can be diverted to a hold-up tank by means of a valve situated in the shower room. After the decontamination procedure, the water in the hold-up tank may be released into the main sewer system if the radiation level is low, or it may be stored for decay if the contaminating materials have a short half life, or it may be pumped

---

Work supported by the U. S. Atomic Energy Commission.

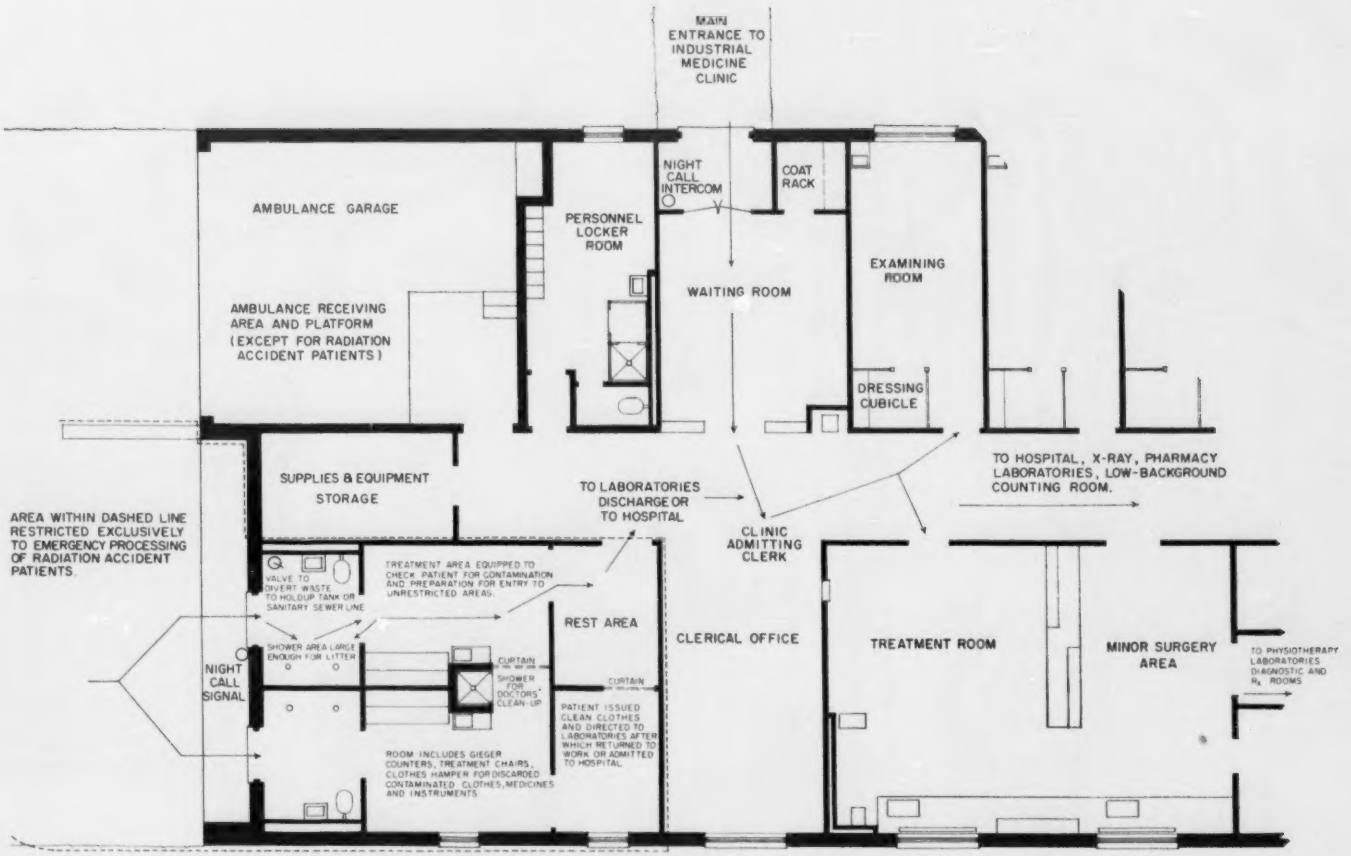

MAIN ENTRANCE TO INDUSTRIAL MEDICINE CLINIC
AMBULANCE GARAGE
AMBULANCE RECEIVING AREA AND PLATFORM (EXCEPT FOR RADIATION ACCIDENT PATIENTS)
PERSONNEL LOCKER ROOM
NIGHT CALL INTERCOM
COAT RACK
WAITING ROOM
EXAMINING ROOM
DRESSING CUBICLE
SUPPLIES & EQUIPMENT STORAGE
TO LABORATORIES DISCHARGE OR TO HOSPITAL
TO HOSPITAL, X-RAY, PHARMACY LABORATORIES, LOW-BACKGROUND COUNTING ROOM.
CLINIC ADMITTING CLERK
AREA WITHIN DASHED LINE RESTRICTED EXCLUSIVELY TO EMERGENCY PROCESSING OF RADIATION ACCIDENT PATIENTS.
VALVE TO DIVERT WASTE TO HOLDUP TANK OR SANITARY SEWER LINE
TREATMENT AREA EQUIPPED TO CHECK PATIENT FOR CONTAMINATION AND PREPARATION FOR ENTRY TO UNRESTRICTED AREAS.
REST AREA
CLERICAL OFFICE
TREATMENT ROOM
MINOR SURGERY AREA
TO PHYSIOTHERAPY LABORATORIES DIAGNOSTIC AND Rx ROOMS
NIGHT CALL SIGNAL
SHOWER AREA LARGE ENOUGH FOR LITTER
CURTAIN
SHOWER FOR DOCTORS' CLEAN-UP
CURTAIN
PATIENT ISSUED CLEAN CLOTHES AND DIRECTED TO LABORATORIES AFTER WHICH RETURNED TO WORK OR ADMITTED TO HOSPITAL
ROOM INCLUDES GIEGER COUNTERS, TREATMENT CHAIRS, CLOTHES HAMPER FOR DISCARDED CONTAMINATED CLOTHES, MEDICINES AND INSTRUMENTS

FIG. 1. Diagram of personnel decontamination unit at Brookhaven National Laboratory.

into a tank truck and processed by some other means to remove the radioactive elements or to concentrate them to a smaller volume for future disposal.

Each unit contains a clothes tree and a large radiation clothes hamper where contaminated clothes can be deposited. The various items can at a later time be separated and handled in various ways according to the amount and type of substances they are contaminated with. If the clothing is contaminated with an element that has a short half life, it may be stored until the level has fallen and then the clothes may be returned. Clothes with longer-lived isotopes may be washed in the hot laundry and returned if, after cleaning, the radiation level is below the acceptable levels. Some articles that are heavily contaminated and that might be difficult to decontaminate, such as leather shoes, may have to be disposed of directly with the hot waste materials.

An attempt is made to keep contaminated wastes separate from noncontaminated wastes by having separate receptacles for the two types of materials. Paper towels used by a contaminated person are discarded in the container marked for radioactive wastes, while paper towels used by a noncontaminated person working in the room are thrown in the ordinary waste disposal can. This cuts down the volume of material that has to be screened for radiation levels before it is disposed of by appropriate means.

The second room of the suite is primarily a treatment room where patients are treated after all the loose external contaminating materials have been removed by the showers or by scrubbing in the sink if only the hands are contaminated. Here simple débridement and wound irrigation can be carried out, dressings applied, and other such procedures done.

The fixed equipment in this room consists of a clean sink, which is kept free of contamination, and cabinets for storage of supplies and instruments. The movable equipment consists of such things as radiation detection counters, a table, a dressing chair, and a high chair used in nasal irrigations after inhalation of contaminating materials.

The cabinets are stocked with such things as solutions for skin decontamination, nasal catheters and syringes for nasal irrigation, instruments for minor surgical procedures, hair clippers for removal of hair contaminated with materials that will not wash out, rubber aprons and gloves for use by personnel who may have to decontaminate unconscious or seriously injured patients, paper slippers, and clean coveralls to issue to subjects after completion of the external decontamination procedures.

The third room contains a litter and a cot and serves as a dressing room. Here the patient is issued clean coveralls and paper slippers, which he puts on prior to leaving through the door into the clinic corridor. He may now be directed or taken to any of the medical department facilities such as the low-level counting room, the room where blood is drawn for various laboratory examinations, the x-ray department, or, if necessary one of the rooms in the hospital for admission.

The flow of traffic through the unit is in one direction from the contaminated to the clean section. The patient enters the shower room directly from the outside and proceeds through the unit without retracing his steps over contaminated regions

until he steps through the door from the third room into the clinic, at which time he should be free of all loose, external, nonfixed radioactive materials.

With the increasing use of radioactive materials and the possibility of contamination in case of war, serious thought should be given to having such a unit or modification of it in our general hospitals. Most emergency rooms are not specifically equipped to handle this type of problem. Without some thought as to how such an incident would be handled, radiation contamination could easily be spread throughout a hospital. While existing facilities can readily be adapted to provide such a unit, it is more difficult to have personnel specially trained and then maintained at a high pitch of efficiency by drill and practice in minor accidents.

The latest advances in Pediatrics

The most complete data on the latest advances in pediatrics, including a critical survey of all important new contributions in this specialty, is presented in

QUARTERLY REVIEW OF PEDIATRICS

Edited by Irving J. Wolman, M.D., with the assistance of an Editorial Board comprising many of the leading pediatricians in the United States, Latin America, Europe, and other areas of the world.

The REVIEW provides a continuous seminar on all aspects of pediatrics, including metabolic and systemic disorders, infections, surgery, public health, nutrition, and psychology.

Published quarterly by:

MD PUBLICATIONS, INC., 30 East 60th Street, New York 22, N. Y.

Subscription rates, including a cumulative cross reference index: 1 year, $11.00; 3 years, $28.00.

The Protective Value of the Middle Ear Reflex

David A. Hilding, Captain, MC, USAR, and*
John L. Fletcher, Captain, MCS, USA†
FORT KNOX, KY.

With the increased interest in the problem of protecting the ear against damage caused by exposure to loud noises has come a correspondingly intensified effort to determine the possible role of the tympanic muscle reflex as a protective mechanism. Since the description of the tensor tympani muscle by Eustachius and the stapedius muscle by Varolius 400 years ago, there has been considerable speculation about their function.

Molinettus[1] wrote that the tensor tympani muscle increases the loudness of weak tones and excludes loud or uncomfortable ones. The relative importance of one or the other of these two functions is still disputed. In his extensive description of the physics and physiology of hearing, published in 1837, Johannes Müller[2] stated that the tensor tympani muscle responds to a loud tone by contracting, thus making the tone less loud. He thought that this effect would be more marked for tones of low pitch. However, he postulated that hearing acuity of deafened persons could be increased by an opening of the Eustachian tube caused by a contraction of these muscles.

A great deal of data has been accumulated since Müller's work, but it was not until quite recently that it was shown that the contraction of the middle ear muscles could protect the hearing apparatus from damage caused by loud noises.[3,4]

ANATOMY

The tensor tympani is a striated muscle about 2 cm. long, which originates from the cartilaginous and bony walls of the Eustachian tube, as well as from the surface of the semicanal that encloses it. Its tendon passes over the cochleariform process of the middle ear, making nearly a right-angle turn to pass laterally to its insertion on the long process of the malleus. The tensor tympani is innervated by the trigeminal nerve through the tensor tympani branch, which arises from the otic ganglion. Its action is to cause the eardrum to move inward.

The stapedius, the smallest skeletal muscle in the body, is buried in a bony case—the pyramidal eminence. Its tendon inserts on the neck of the stapes, and its innervation is derived from the facial nerve by means of a small branch, the stapedial nerve. When the stapedius contracts, it pulls the head of the stapes posteriorly.

PHYSIOLOGY OF THE TYMPANIC MUSCLE REFLEX

Consensual Nature of Reflex. Stimulation of one ear by a sound of sufficient energy and proper frequency results in a muscle contraction in both ears. Apparently the contraction is identical regardless of which ear is stimulated. Pollak[5] was the

* Ear, Nose, and Throat Section, Ireland Army Hospital, Fort Knox, Kentucky.
† Former address: Psychology Division, United States Army Medical Research Laboratory, Fort Knox, Kentucky. Present address: Central Institute for the Deaf, St. Louis.

first investigator able to show this, in his dog experiments in 1886. This phenomenon has greatly facilitated experimentation, since observation of the reflex can be carried out in the ear opposite to the one being stimulated.

Latent Period. The latent period can be defined as the period between the arrival of the stimulating tone at the ear and the contraction of the muscle. However, there is dispute on whether it is correct to measure the time of arrival of the sound at the eardrum or at the beginning of the effective stimulus, such as the onset of the cochlear microphonics. Most investigators measure from the start of the stimulating tone itself. The moment of the beginning of muscle contraction, the achievement of maximum contraction, or some point in between can be chosen as the end of the latent period. For many years it has been known that this period varies somewhat with the magnitude of the stimulating tone. The latent time is less with a more intense tone, as shown by Lorente de No′,[6] Metz,[7] and others.

Kato,[8] in 1913, was one of the first to measure the reflex time accurately. He developed a delicate optical and electric system that showed latencies of about 20 milliseconds. Many research workers have developed other means of measuring this aspect of the problem, but perhaps the most complete data were presented by Wersäll,[9] who meticulously measured the tension of the muscle tendon, as a function of time, with tones of various intensities and published curves defining the latent period of the reflex. The results showed that the mean duration of latency, measured from the onset of the stimulus to the first sign of contraction, was 10 milliseconds for the stapedius and 16 milliseconds for the tensor tympani muscle, with a sound stimulus of 135 decibels (re 0.0002 dyne/sq. cm.) at 1000 cycles/second. The period from the onset of the stimulating tone to attainment of 50 per cent maximum tension was 43 milliseconds for the stapedius and 61 milliseconds for the tensor tympani muscle. Measuring time to achieve maximum tension gave 63 milliseconds for the stapedius and 132 milliseconds for the tensor tympani muscle.

Reflex Threshold. There are problems of definition associated also with describing the reflex threshold. Many workers have reported values in terms of decibels above normal hearing, although it is probably more customary to use the reference level of 0.0002 dyne/sq. cm. In addition, the method used to judge the contraction is obviously a variable influencing the results obtained.

In 1933, Lorente de No′ and Harris[10] obtained a threshold of 50 decibels for the stapedius and 80 decibels for the tensor tympani muscle in decorticated rabbits. These workers judged the contractions by direct microscopic examination and used the findings in 4 persons with normal hearing as a reference level in reporting their data.

In 1935, Hallpike,[11] using decerebrated cats, observed contractions at a sound intensity of about 70 decibels above human threshold. Wever and Vernon[12] noted diminution in the cochlear microphonic produced by a contralateral stimulation of the reflex in the cat. They obtained values that can be transposed to 80 to 100 decibels above 0.0002 dyne/sq. cm. Wersäll's[9] myographs indicated that the first increase in the tension of the stapedius muscle occurred with levels of 81 to 107 decibels and of the tensor tympani muscle, 98 to 115 decibels. (These values are also in reference to 0.0002 dyne/sq. cm.)

Lüscher[13] made use of existing eardrum perforations in human beings to study the characteristics of the stapedius reflex, but since the audiometer was not available to him, he could not give quantitative data about the threshold. However, a few years later, Lindsay, Kobrak, and Perlman[14] were able to make audiometric measurements of the sensitivity of the reflex, observing motion of the muscle tendon through perforations. Thresholds varied between 65 and 90 decibels in the subjects tested.

Another method of judging the activity of the acoustic reflex in human beings is to measure the change in the impedance of the eardrum produced when the reflex is stimulated. This method, developed by Metz,[7] was recently used by Jepsen[15] to estimate the threshold. He obtained changes in impedance at 70 to 90 decibels above normal threshold.

Fatigability of Reflex. Kato[8] observed that the tensor tympani muscle is more easily fatigued than the stapedius. Lüscher[13] studied fatigue of the reflex in human subjects with eardrum perforations and found that after 30 to 70 seconds' stimulation with the Galton pipe, the reflex fatigued. However, if a new tone of a different frequency was introduced, the muscle once again contracted. He also showed that after the stapedius muscle was completely fatigued, it required two to three minutes to recover its sensitivity to the tone used to fatigue it. Kobrak, Lindsay, and Perlman,[16] in their observations of human ears, as well as in studies of rabbits anesthetized with urethan or operated on under local anesthesia, were able to confirm Lüscher's observation that a tone different from the fatiguing tone would reactivate the reflex. Wersäll[9] studied this phenomenon in more detail and found that the second tone could reactivate the reflex only if it differed in frequency from the original tone by a sufficient amount. For instance, the fatigue produced by a 1000 cycles/second tone "spread" to 2100 cycles/second; however, with a wider frequency difference, a contraction of almost equal force could be produced with the second tone.

Muscle Tension. Utilizing electrical stimulation of the muscles, Wever, Vernon, and Lawrence[17] were able to demonstrate tension of about 4 Gm. for the tensor tympani and 1.6 Gm. for the stapedius muscle. Wersäll,[9] using acoustic stimulation and a more refined technique, obtained maximum values of approximately 11.5 Gm. in the stapedius and 8.9 Gm. in the tensor tympani muscle.

Attenuation of Sound. Under light allobarbital-urethan anesthesia, there are regular spontaneous contractions of the muscles. These were used by Wiggers[18] to study the maximum attenuation produced by the middle ear reflex. He found that the apparent attenuation at the lower frequencies was as much as 45 decibels. Attenuation was determined by the diminution of the cochlear microphonic. There was much less attenuation for the higher frequencies, and at 1500 cycles/second the transmission of sound was slightly increased (as predicted by Müller[2] in 1837).

Wever and Vernon[20] studied this question in detail and found maximum attenuation of 20 decibels for the lower tones. At less intense levels of stimulation, however, they were able to demonstrate a definite increase in sound transmission. In some cases this increase in sound transmission was related to a decrease in muscle tension, in others to a small increase. They felt that the decreased tension probably decreases damping and thus increases transmission, while a slightly increased tension may also facilitate transmission by decreasing looseness in the coupling of the ossicular joints.

Both of these studies utilized changes in cochlear microphonics for estimating the transmission characteristics of the reflex.

In unanesthetized cats, Galambos and Rupert[4] found maximum attenuation of 20 to 22 decibels, as measured with cochlear microphonics.

By another method, Simmons[21] showed an attenuation of 15 decibels. He used cats with chronically implanted round window electrodes and compared the voltage of the cochlear microphonic while the animal was awake with the voltage when it was under deep anesthesia. The paralysis of the muscles induced by deep anesthesia caused an increase in voltage of 15 decibels when the ear was stimulated by 80 decibels of sound. If the stimulation was only 40 decibels, the increase was 5 decibels.

With these data from animal studies, it is surprising that Loeb and Riopelle[22] were able to demonstrate a change in human threshold of only about 3 decibels with contralateral stimulation of the reflex. However, they later used a modification of the alternate binaural loudness balance test and found that attenuation seemed to be greater at levels well above hearing threshold.* In other words, the reflexive protective action is not a threshold phenomenon, merely putting in attenuation, but is more comparable to a governor, going into action at the appropriate level.

PROTECTIVE FUNCTION OF TYMPANIC MUSCLE REFLEX

The first evidence that there is less damage in ears protected by the muscles of the middle ear was published by Taruya[23] in 1953. He studied the histological changes in rabbit cochleas produced by a series of explosions of "cracker balls." In one ear of each animal he had cut the tendon of the tensor tympani or stapedius muscle. He found more damage in the inner ear on the side that had a divided tendon. However, the passive support of the muscle tendon is probably responsible for this protection, since the muscles would not be expected to contract effectively in the extremely short period of time during which the explosion would last.

Galambos and Rupert[4] were able to prepare cats with electrodes permanently in contact with the round window. These preparations permitted continuing recording of cochlear microphonics, without anesthesia, over a period of time. A similar technique for round window implantation in awake animals was developed by Legouix[25] in guinea pigs and Radionova[26] in hens.

Galambos and Rupert showed that the temporary depression of the cochlear microphonic produced by exposure to loud tones (2000 cycles/second at 85 decibels for three minutes) was much more severe in animals with the middle ear muscles cut. They carefully pointed out that this experiment did not show whether the protection offered by the muscles is due to the passive support of the muscle or to active contraction.

That protection is afforded by an active contraction is strongly suggested by the data reported by Fletcher and Riopelle.[3] They recently completed a study designed to permit the auditory evaluation of the effect of artificially stimulating the acoustic reflex just prior to the noise of a gun being fired. As pointed out by Tatsuka, Naka-

---

* Personal communication.

mura, and Kirkikae,[27] the latent period of the middle ear reflex would normally make it inoperative as a means of protection against a loud, sharp blast, such as the sound of a gun, because the energy of the sound would reach the inner ear during the latent period of the muscles. Fletcher and Riopelle produced temporary threshold shifts in human subjects by exposing them to the sound of 100 rounds fired singly from a 30 caliber machine gun. The findings were compared with the threshold shifts produced by the same number of rounds, but with each shot preceded by a 98 decibel, 1000 cycles/second tone of 200 milliseconds' duration. This short tone was apparently sufficient to stimulate contraction of the middle ear muscles, for a marked degree of sound protection was obtained. There was much less shift in threshold when the subjects were protected with the tone. The degree of protection was compared with that afforded by the V-51R ear defender (a soft plastic ear plug) and found to be of about the same order of magnitude.[28]

Additional experiments are now being carried out in order to demonstrate further that this effect is dependent on the presence of the muscles. Cats have been prepared as described by Galambos and Rupert,[4] some having had the tendons of the middle ear muscles divided, and these animals will be exposed to gunfire with and without the "protective tone."[29]

SUMMARY AND CONCLUSIONS

Characteristics of the stapedius and tensor tympani muscles have been discussed. When a tone is presented to either ear, if its intensity is above threshold of the reflex, the stapedius and tensor tympani muscles of both ears will contract. A latent period of about 10 milliseconds occurs between the arrival of the sound at the ear and the onset of effective contraction. After constant stimulation, the reflex becomes fatigued, but a tone of considerably different frequency can induce a new contraction.

It has been established that contraction of the middle ear muscles provides considerable attenuation of sound transmission through the middle ear. Also, it has been demonstrated that severing the tendons makes the ear more sensitive to loud noises. There is strong evidence to support the concept that contraction of the muscles is a protective mechanism, but further work is needed to prove it definitely.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Drs. R. Galambos and H. Davis for their generous and helpful criticisms and suggestions.

BIBLIOGRAPHY

1. Morgagni, J. B.: Epistolae Anatomicae, Patavii, 1764. Cited by Wever and Vernon.[20]
2. Müller, J.: Handbuch der Physiologie des Menschen, Coblenz, J. Hölscher, 1837, II Abt. 1, pp. 435–441.
3. Fletcher, J. L., and Riopelle, A. J.: The Protective Effect of the Acoustic Reflex for Impulsive Noise, USAMRL Report. In press.
4. Galambos, R., and Rupert, A.: Action of the middle ear muscles in normal cats, J. Acoustics Soc. Am. *31*:349–355, 1959.
5. Pollak, J.: Über die Function der Musculus Tensor Tympani, Med. Jahrbücher, Neue Folge *1*:555, 1886. Cited by Wersäll.[9]

6. Lorente de No′, R.: The reflex contractions of the muscles of the middle ear as a hearing test in experimental animals, Tr. Am. Laryng., Rhin. & Otol. Soc. *39*:26–42, 1933.
7. Metz, O.: Studies on the contraction of the tympanic muscles as indicated by changes in the impedance of the ear, Acta oto-laryng. *39*:397–405, 1951.
8. Kato, T.: Zur Physiologie der Binnenmuskeln des Ohres, Pflüger's Arch. f. d. ges. Physiol. *150*:569–625, 1916.
9. Wersäll, R.: The tympanic muscles and their reflexes, Acta oto-laryng., suppl. 139, 1958.
10. Lorente de No′, R., and Harris, A. S.: Experimental studies in hearing. I. The threshold of the reflexes of the muscles of the middle ear. II. The hearing loss after extirpation of the tympanic membrane, Laryngoscope *43*:315–350, 1933.
11. Hallpike, C. S.: On the function of the tympanic muscles, J. Laryng. & Otol. *50*:362–367, 1935.
12. Wever, E. G., and Vernon, J. A.: The threshold sensitivity of the tympanic muscle reflexes, A. M. A. Arch. Otolaryng. *62*:204–213, 1955.
13. Lüscher, E.: Die Funktion des Musculus Stapedius beim Menschen. II Mitteilung: Reflexauslosung durch Knochenleitung, Ermüdung, und Erholung des Reflexes, Ztschr. Hals-Nasen u. Ohrenheilk. *25*:462–478, 1930.
14. Lindsay, J. R.; Kobrak, H., and Perlman, H. B.: Relation of the stapedius reflex to hearing sensation in man, Arch. Otolaryng. *23*:671, 1936.
15. Jepsen, O.: The threshold of the reflexes of the intratympanic muscles in a normal material examined by means of the impedance method, Acta oto-laryng. *39*:406–408, 1951.
16. Kobrak, H. G.; Lindsay, J. R., and Perlman, H. B.: Experimental observations on the question of auditory fatigue, Laryngoscope *51*:798, 1941.
17. Wever, G. B.; Vernon, J. A., and Lawrence, M.: The maximum strength of the tympanic muscles, Ann. Otol., Rhin. & Laryng. *64*:383–391, 1955.
18. Wiggers, H. C.: The functions of the intra-aural muscles, Am. J. Physiol. *20*:771–780, 1937.
19. Wever, E. G., and Vernon, J. A.: The effects of the tympanic muscle reflex upon sound transmission, Acta oto-laryng. *45*:433–439, 1955.
20. Wever, E. G., and Vernon, J. A.: The control of sound transmission by the middle ear muscles, Ann. Otol., Rhin. & Laryng. *65*:5–14, 1956.
21. Simmons, F. B.: Middle ear muscle attenuation at moderate sound levels, Fed. Proc. *18*:573, 1959.
22. Loeb, M., and Riopelle, A. J.: Influence of Loud Contralateral Stimulation on the Threshold for Lower Frequency Tones, USAMRL Report. In press.
23. Taruya, T.: Studies on the function of the intrinsic ear muscles, Hiroshima J. M. Sc. 2:245–268, 1953.
24. Taruya, T.: Studies on the function of the stapedial muscle of rabbit, Hiroshima J. M. Sc. 2:351–360, 1954.
25. Legouix, J. P.: Technique d'enregiotrements des potentials cochlaires, sur l'animal éveil, Compt. rend. Soc. de biol. *151*:218–222, 1957.
26. Radionova, E. A.: Electrical potentials in the peripheral part of the auditory analyser: an investigation under chronic experiment conditions, Fiziol. zhur. *44*:839–847, 1958.
27. Tatsuka, G.; Nakamura, K., and Kirkikae, I.: Studies of the acoustic reflex. Part I. Electromyographic studies of the acoustic and auricular reflex, Ann. Otol., Rhin. & Laryng. *63*:939–949, 1954.
28. Fletcher, J. L.: Comparison of Attenuation Characteristics of the Acoustic Reflex and the V-51R Earplug, USAMRL Report no. 397, 1959.
29. Hilding, D. A.: The tympanic muscle reflex as a protective mechanism against loud impulsive noise, Ann. Otol., Rhin. & Laryng. In press.

A Clinical Evaluation of Fluphenazine

William D. Gray, M.D.
SALISBURY, MD.

Prominent among the reported properties of the phenothiazine derivatives are their ataractic action and antiemetic effect.[1–4] As anxiety and emesis are symptoms commonly seen in present-day practice, a drug that will relieve both may prove to be extremely useful.

Recently, a new phenothiazine, fluphenazine (Prolixin*), was introduced for clinical investigation. From experimental studies[5] and preliminary clinical trials,[6] fluphenazine appears to be pharmacologically active in remarkably low dosages.

A study was undertaken to evaluate fluphenazine in the treatment of patients with anxiety and in the control of vomiting and nausea. The findings reveal the potential usefulness of the drug in everyday practice, as is evident from the following report.

METHODS AND MATERIALS

The Patients. A total of 152 patients were treated with fluphenazine in the course of this study. Twenty-six were male and 126 were female patients. They ranged in age from 19 months to 80 years, although only 2 of the patients were children. Fluphenazine was prescribed to 70 of the 152 patients for its ataractic effects, and it was given to 82 patients to control nausea and vomiting. The indications in the 70 patients given the medication for its ataractic effects included a variety of mental and emotional disturbances typical of those seen daily by the practicing physician, including anxiety reactions, domestic difficulties, employment duties, and other environmental stresses. Specifically, 33 of the 70 patients presented patterns of symptoms, in the absence of any organic cause, such as crying spells, insomnia, palpitations, vague precordial pains, and a general feeling of restlessness, nervousness, and tenseness. In 18 additional patients among these 70, similar symptoms prevailed accompanied by such physical ailments as heart disease, arthritis, hypertension, premenstrual tension, the menopausal syndrome, senility, and arteriosclerotic brain syndrome, while 15 other patients exhibited considerable psychic stress in their complaints of anxiety, depression, panic, confusion, sensations of choking, "flapping diaphragm," and other psychoneurotic symptoms. Two patients were troubled with postalcoholic tension. The two children in the series were treated with fluphenazine because of extreme nervousness or behavior problems.

Of the 82 patients suffering from nausea and vomiting, 43 were pregnant and 24 were postoperative patients; in the remaining 15 the emesis was of varied etiology. In the nonsurgical patients, nausea had recurred at frequent intervals or had been continuously present for periods varying from two hours to eight months.

Administration of the Drug. Fluphenazine was administered as an ataractic agent in total daily dosages of from 1 to 7.5 mg., always by mouth and never in excess

* The trade name of E. R. Squibb & Sons Division, Olin Mathieson Chemical Corp., for fluphenazine is Prolixin. Fluphenazine was supplied for this study by this firm.

TABLE I

Clinical Response of 70 Patients to the Ataractic Action of Fluphenazine

Condition	No. of patients	Dosage of fluphenazine, mg./day*	Duration of therapy	Therapeutic response				Side effects, no. of patients
				Excellent	Good	Fair	Poor	
Anxiety and/or tension states	33	2 to 7.5	1 wk. to 2 mo.	27	3	1	2	8
Psychosis (ambulatory) or psychoneurosis	15	1 to 5	2 to 6 wks.	11	1	0	3	2
Somatic conditions complicated by emotional stress	18	2 to 5	6 days to 8 mo.	14	3	0	1	1
Postalcoholic tension	2	4	3 days	2	0	0	0	1
Pediatric agitation or behavior problem	2	2 to 5	1 to 2 mo.	2	0	0	0	0
Total	70			56	7	1	6	12

* Administered orally in 1, 2, or 3 doses daily of 1, 2, or 2.5 mg./dose.

of 2.5 mg. as a single dose. Therapy lasted in these cases for from one week to eight months, as indicated, and in some cases treatment was still being continued at the time of this report. Fluphenazine was administered to control emesis either orally, intramuscularly, or by rectum, in total daily dosages of from 1 to 5 mg., single doses never exceeding 2.5 mg. Treatment was continued as indicated, some patients receiving only a single dose and others being treated for as long as two months.

Evaluation of Response. The responses of the patients to therapy were graded as excellent, good, fair, or poor, depending on the degree of improvement shown or the absence of any change. The response was considered to be excellent if the patient became essentially symptom free and to be good if he improved enough so that symptoms were no longer a problem, while a fair response indicated only slight improvement. The response was considered to be poor if treatment failed to provide any relief or if the patient felt worse.

RESULTS

The effects of fluphenazine on anxiety and other states of emotional or mental instability are summarized in table I. A good or excellent therapeutic response was gained in 63 of the 70 treated patients (90 per cent), a fair response was seen in 1 patient, and in the remaining 6 patients treatment failed. Improvement, when it occurred, was seen early, with the patients feeling less irritable and tense, and more relaxed. Treatment was continued in half of the patients for only two or

TABLE II

Clinical Response of 82 Patients to Antiemetic Action of Fluphenazine

Condition	No. of patients	Dosage of fluphenazine, mg./day*	Duration of therapy	Therapeutic response				Side effects, no. of patients
				Excellent	Good	Fair	Poor	
Nausea and vomiting associated with pregnancy	43	2 to 6	1 dose to 2 mo.	41	1	1	0	1
Nausea and vomiting, postoperative	24	2 to 4	1 dose to 3 wk.	23	1	0	0	0
Nausea and vomiting associated with a variety of conditions	15	1 to 4	1 dose to 1 mo.	15	0	0	0	0
Total	82			79	2	1	0	1

* Administered orally, rectally, or intramuscularly as 1, 2, or 3 doses daily of 1, 1.25, 2, or 2.5 mg./dose.

three weeks, or even less. In a number of cases, the patients felt much better after two or three days on the drug but the medication was continued for several weeks or several months because symptoms returned when it was withdrawn, or else the patients desired to continue the medication. In some cases, improvement was obtained only after therapy had been continued for several weeks with careful adjustment of dosage.

The effectiveness of fluphenazine in controlling nausea and vomiting is summarized in table II. Symptoms were completely relieved in 79 of the 82 patients treated (96 per cent), while in 2 they were considerably eased though vomiting tended to recur occasionally, and in 1 patient, only fair improvement was obtained. Relief was usually prompt, in some cases within 15 to 30 minutes after the drug was first given, usually by injection, but in several instances when given by rectum or by mouth. A single dose sufficed in 23 cases, principally among postoperative patients. Although pregnant patients generally obtained prompt relief, medication was continued for relatively longer periods to prevent recurrence of nausea. Relief was obtained in an equally high proportion of cases, regardless of the cause of emesis.

A total of 13 patients in the entire series complained of side effects, including "jitteriness," restlessness, drowsiness, agitation, "deadened senses," and transient dizziness. In 4 of these, medication was withdrawn because the patient felt so uncomfortable (see table III). However, the remaining patients showing reactions were continued on treatment, although in all but 2 the dosage was reduced.

Case Reports. The following case reports are representative of this series.

Case 1. A 35-year-old woman was admitted to hospital for hysterectomy because of extensive endometriosis. Three years previously she had experienced severe postoperative nausea and vomiting that persisted despite a variety of measures undertaken for their relief. After surgery the patient began to retch and was immediately given 2.5 mg. of fluphenazine intramuscularly. The retching stopped within 20 minutes. Fluphenazine was continued, 1 mg. every eight hours. The postoperative course was uneventful without recurrence of retching, nausea, or vomiting.

TABLE III

Side Effects in 70 Patients with Mental and Emotional Disturbances or Emotional Stress Treated with Fluphenazine

Side effect	No. of patients	Remarks
"Jitteriness"	5	Drug discontinued in 3 patients and dosage reduced in 2
Restlessness	1	Drug withdrawn because patient did not improve clinically
Drowsiness	3	Dosage reduced in 1 patient and drowsiness cleared after day or so in the other 2 patients as treatment was continued
Agitated	1	Patient was agitated before therapy and became more agitated and depressed after treatment was begun; after dosage was reduced he felt better and less tense and stopped screaming
"Deadened senses"	1	Dosage reduced
Transient dizziness	2	

Case 2. For the previous 10 years, a 46-year-old woman had been treated intermittently for acute anxiety with parenteral barbiturates and a variety of ataractic drugs with only fair results. The attacks of anxiety lasted three or four days despite the medication given. On the occasion of the present attack she was placed on fluphenazine, 3 mg. daily, then 2 mg. daily for three months. During that time she was seen only when the medication was all used. At each visit she said she felt better than she had in 10 years.

Case 3. A 19-year-old man with schizophrenia had received previous treatment with high dosages of another phenothiazine and had improved sufficiently to be discharged from the hospital. After one week he had discontinued the prescribed medication and had a recurrence of the former symptoms of withdrawal, psychomotor retardation, autistic preoccupation, and marked hostility, especially to his family. At the present admission to the hospital, he was given fluphenazine, 2.5 mg. orally each day. Within three days he became less withdrawn, showed more interest in his surroundings, and was much less hostile to his family. After four days he was discharged. Fluphenazine (2.5 mg. daily) has been continued at home for a period of four months without recurrence of symptoms.

COMMENT

The therapeutic results obtained with fluphenazine in the low dosages employed in this study are impressive, and they reveal the strong ataractic and antiemetic properties of the drug. Moreover, its efficacy in most cases when given in one or two doses a day was a distinct advantage in the treatment of ambulant patients, for whom convenient dosage is essential to successful therapy. The infrequency and mildness of reactions encountered indicate that fluphenazine is safe and suitable for use in outpatients.

The general sense of relaxed well-being induced by fluphenazine was of definite benefit in the anxious, tense patient. Also gratifying was the apparent change in the reactions of these patients to situations that remained unchanged. Home troubles and other problems did not seem to bother them as much as formerly.

The efficacy of fluphenazine in relieving nausea and vomiting was striking. Not only was the drug effective in 96 per cent of cases treated, but relief of symptoms

was obtained promptly, without unpleasant side effects, and was maintained by only one or two doses a day, where indicated. Altogether, the findings here indicate that fluphenazine is a superior antiemetic agent.

SUMMARY

Fluphenazine has been administered to a total of 152 ambulant patients in daily dosages of 1 to 7.5 mg., as 1, 2, or, in some cases, 3 doses a day of 1, 1.25, 2, or 2.5 mg. each. To 70 of the 152 patients, fluphenazine was prescribed as an ataractic agent, with 90 per cent becoming symptom free or improving so that the symptoms of anxiety, nervousness, and tenseness were no longer disabling. To 82 of the 152 patients in the series, fluphenazine was given to control nausea and vomiting. Of these, 96 per cent became symptom free and remained so on 1 or 2 doses of the drug each day.

The findings of this study indicate that fluphenazine is a highly potent drug with strong ataractic and antiemetic properties. Its effectiveness in low dosage levels, when administered under a convenient dosage schedule, and the low frequency of unpleasant side reactions accentuate the potential usefulness of fluphenazine for the general practitioner.

BIBLIOGRAPHY

1. Gold, M. I.: Tranquilizing drugs, Am. Pract. & Digest. Treat. *10*:241, 1959.
2. Ayd, F. J., Jr.: Tranquilizing drugs in private practice, New York J. Med. *10*:1742, 1957.
3. Preisig, R., and Landman, M. E.: Use of perphenazine in anxiety states and hyperemesis, Am. Pract. & Digest. Treat. *9*:740, 1958.
4. Moyer, J. H., et al: Clinical studies of an anti-emetic agent, chlorpromazine, Am. J. M. Sc. *228*:174, 1954.
5. Burke, J. C., and Linegar, C. R.: Pharmacology and toxicology of SQ4889, 4918 and 4924. *In:* Laboratory Reference Manual, New Brunswick, N. J., The Squibb Institute for Medical Research, 1957.
6. Darling, H. F.: Fluphenazine: A preliminary study, Dis. Nerv. System *20*:167, 1959.

FTC Acts Against Arthritis Book

The Federal Trade Commission recently ordered publishers of the book *Arthritis and Common Sense* to stop making certain advertising claims about the treatment of arthritic disorders. The complaint directs that publishers stop representing that theories advocated in the book will have beneficial effects in arthritis and rheumatic fever. FTC says more than 500,000 copies of the book, published by Witkower Press, Inc., Hartford, Connecticut, have been sold in recent years.

Notes on the Hallucinogenic State

Sidney Cohen, M.D.

BRENTWOOD NEUROPSYCHIATRIC HOSPITAL, VETERANS ADMINISTRATION
LOS ANGELES, CALIF.

HISTORICAL BACKGROUND

Psychotomimetic drugs are no new group of agents—anthropological lore is pervaded with tales of hallucinogens, phantastica, and deliriants. It seems that every culture has sought out plants that might enable the user to change his level of awareness and briefly leave everyday reality. A surprising number of tribes found some berry, root, mushroom, or cactus that produced dissociation. Those to whom such pharmacological aids were unavailable developed practices of sensory isolation (as in the Egyptian temple rites), fasting and physical depletion (e.g., the Sioux sun ritual), or even mutilation (e.g., self-flaying by the Blackfoot Indian) to achieve temporary alterations of consciousness.

The two medicaments that have finally come to be most popular on a global basis are rather unfortunate choices. One is the narcotic, opium, and the other, the anesthetic, alcohol. Neither is a truly psychotomimetic substance, but they do bring forth an intoxication that is reminiscent of the hallucinogenic state. The phase of dilated awareness, intensified perception, and heightened affect is relatively brief with distillates of the poppy and the grape. The intervening confusion or torpor is more characteristic of these anodynes of the East and West.

The story of the hallucinogens is a long one and only the briefest mention of the better-known drugs of this class can be made here. It properly begins with *Soma pulari*, the legendary Indo-Persian potion, which, when properly brewed and drunk, "made one a god." What is called *Soma pulari* today is not the plant of the ancients, or else its alkaloids have become attenuated over the centuries.

The *Odyssey* describes a "banisher of sorrow" called nepenthe. This was not opium, which the Greeks also knew and used for insomnia. Nepenthe may have been imported from Egypt and was highly thought of in the eastern Mediterranean region. This Homeric grief-reliever is also lost to present-day pharmacology.

Hashish (marihuana, Indian hemp, *Cannabis sativa*) has a strange and varied history. On the one hand, yogis and other contemplatives used it as an aid in achieving a condition of selfless meditation; on the other, it was given to thugs and assassins to foster large-scale garroting and strangulation. Today, it is smoked by maladjusted teen-agers for "kicks" and is supposed to predispose them to heroin addiction. Its current reputation is such that serious psychopharmacological investigation of this non-indolic hallucinogen is not even attempted.

The toxic *Amanita muscaria*, the fly agaric, was nibbled by tribesmen along the northern tier of the Eurasian land mass. On the dreary Kamchatkan peninsula, the Koryak nomads found that when they partook of a measured amount of the spotted mushroom, a colorful fantasy world was theirs for a few hours. How they discovered that the urine of the mushroom-eater was likewise hallucinogenic is quite

unknown. The Siberian enjoyed his intoxication quietly seated on the floor of his hut. The bearskin-clad Scandinavian berserker is supposed to have chewed the *Amanita* to achieve a superhuman strength and reckless courage. The prayer of the medieval Christian, "From the intolerable fury of the Norsemen, oh Lord, deliver us," may have been due in part to a drug-induced rage.

The recently rediscovered *Psilocybe mexicana* is employed in a semireligious setting in southern Mexico. Less than three years after Wasson had eaten the mushroom in a curandera's dark hut, Hofmann succeeded in synthesizing its alkaloid, psilocybin, in the Sandoz Laboratories in Basel. Like many other hallucinogenic compounds, it is an indole; specifically, it is 4-phosphoryl hydroxytryptamine.

The snuff of cohoba (*Piptadenia peregrina*) is inhaled by Central and South American natives to achieve states of religious or social union. One of the active ingredients is bufotenin, a dimethyl derivative of serotonin. Serotonin commands considerable interest, for it is considered to be a cerebral synaptic transmitter with important implications in emotional disorders. Bufotenin is also found in *Amanita muscaria* and in poisonous toad's skin, hence its name.

A closely related chemical, dimethyltryptamine, is also known to have a psychotomimetic action, as was demonstrated by St. Szara[1] recently. Dimethyltryptamine is one of the active elements of yajé, a decoction favored in the Caribbean islands.

In the Belgian Congo the Bantu give young men the roots of *Tabernanthe iboga* to chew as part of their initiation into the secret societies. According to Garrett,[2] these are cults of ecstacy, ecstacy induced by the *iboga*. However, in our experience with the alkaloid ibogaine, the autonomic and somatic side effects were more impressive than any psychic property.

The peyote button, which contains mescaline, must be mentioned because it is among the more active and well known of the naturally occurring hallucinogens. Growing as a small cactus in the watershed of the Rio Grande, it is revered by Indians of the Native American Church from Mexico to Canada. At spaced occasions they chew the buttons in a nightlong, ritualized ceremony. They are convinced that the peyote, bitter as it is, brings visions of God, binds the group together as brothers, cures them of a variety of physical ailments, and keeps them away from the curse of firewater.

The fantastic imagery induced by peyote is not restricted to primitive peoples. Sophisticated experimenters like Weir Mitchell, Havelock Ellis, and Aldous Huxley have set down fascinating accounts of their mescaline experiences. Multicolored visual illusions and hallucinations, intensification of the perceived object, and changes in ego identity were the most prominent alterations reported.

One could go on to speak of *Datura tolloache*, *Bannisteria caapi*, mandrake, telepathine, olouiqui, and many others. Each subculture appears to have sought out its own psychic transformer and prized it for its ability to allow the user to explore the recesses of his mind and to transcend himself for a while.

Hoffer[3] and Osmond[4] contended that some aberrant metabolic derivatives of epinephrine such as adrenochrome are capable of evoking subtle but definite dissociation states. Such data have important implications, for these are the first psychotomimetic substances to be found in human intermediary metabolism. It is specu-

lated that the schizophrenic syndrome may have, as its biochemical representation, a deviant pathway for degrading endogenous epinephrine.

In 1943 Hofmann and Stoll added the diethylamide group to lysergic acid obtained from rye ergot and synthesized the most potent and reliable of the hallucinogenic series. It is doubtful that the apocryphal epidemics of madness recorded in European villages were due to eating of spoiled rye, for lysergic acid itself has no psychic activity. Ergotism certainly would occur under these conditions, but outbreaks of widespread bizarre behavior were probably the result of hysterical dissociative reactions disseminated by suggestion.

The configuration of d-lysergic acid diethylamide (LSD_{25}) is specific for its cerebral activity; the levorotatory compound is completely inert in this respect. Many further modifications of lysergic acid have been produced in the Sandoz Laboratories but none exceed LSD_{25} in activity by weight. Marked serotonin antagonism is characteristic of LSD_{25} and some of the other congeners, but a direct relationship between this property and the psychological manifestations does not exist.

The phenomenal potency of LSD_{25} should be considered as a matter of interest. After oral doses of 1 μg./Kg. substantial drug effects can be noted over an eight-hour period. As little as $\frac{1}{4}\gamma$/Kg. will evoke a minimal autonomic and psychic response. The intravenous dose is even lower because the vagaries of gastrointestinal absorption are bypassed. Only drugs like ouabain and ergotamine approach this potency, but their minimal effective dose is five times that of LSD_{25}.

Tracer studies with isotopically labeled LSD_{25} indicate that the brain receives no more than its share compared with average tissue distribution. One hour after ingestion the central nervous system has been cleared of the drug. It is at this time that the psychic manifestations begin. This means that less than 1 μg. of LSD_{25} briefly in contact with the brain mass can activate the very substantial changes to be described.

It now appears that hallucinogens need not be indoles or potential indoles (like mescaline); synthetics with a variety of structures are being included in this category. These are represented by the piperidyl benzilates and the cyclohexylamines.

DEFINITIONS

Now that our neurochemists are working toward the avowed aim of interfering with cerebral function and producing psychic disruption, it may be well to redefine "hallucinogenic" and "psychotomimetic." These terms should be restricted to agents that induce varying degrees of ego dissolution, perceptual distortions, variations in mood, and marked alterations of the thinking process without producing confusion or disorientation. "Hallucinogen" is a rather unfortunate name for this class of agents, for true hallucinations occur only rarely; "illusinogen" or "pseudohallucinogen" would actually be more accurate. Likewise, "psychotomimetic" describes only a part of the potential activity of drugs like LSD_{25}. Temporary psychoses can certainly be provoked, but states quite unlike psychotic reactions have also been manifested. These may even be highly integrative conditions in which total attention can be focused, the peripheral distractions are extinguished, and

integral thought becomes possible. The semantically loaded "psychotomimetic" might properly give way to Osmond's[4] "psychedelic," mind-manifesting, a neutral term that simply indicates that mental changes take place.

Almost every drug used in medicine can precipitate a delirium when given in excess or to hypersensitive persons. This is a toxic confusional state and, despite the occasional presence of hallucinatory phenomena, should not be considered in the group under discussion. Anticholinergics, sedatives, narcotics, steroids, and stimulants are drugs that are more likely to produce these aberrant mental reactions.

Naturally, an overlap exists. Psychedelics given in large amounts may engender confusion, and occasionally deliriants will cause a reaction indistinguishable from the chemically induced "model psychoses."

THE PSYCHEDELIC STATE

A description of the effect of drugs of this group on normal subjects is based on our observations with LSD_{25}. Any attempt to communicate the total LSD_{25} experience will surely fail. Much of it occurs on a nonverbal level and it is so highly variable that an over-all statement will not encompass the entire spectrum of possible reaction forms. Furthermore, it is so foreign to everyday existence that our vocabulary is lacking in words to describe precisely even that which could be described. Therefore, a breakdown of the condition into some of its components might have more value. However, it is admitted that a synthesis of the parts will not re-create the whole.

What is the quality of the LSD_{25} experience? The perceptual alterations are most striking and most easily described. Perhaps the first change is a lightening of the "screen." Ordinarily, with closed eyes one sees a gray-black expanse. A few minutes to a half hour after LSD_{25} is taken, this becomes lighter as though one were looking at a bright light through the closed eyelids. Soon thereafter a kaleidoscopic flow of geometrical designs, elaborate patterns, or structured images in saturated colors may appear. These elementary hallucinations will change with external stimuli such as sounds or odors (synesthesia) or with internal stimuli such as mood swings. Prolongation of the afterimage may be so pronounced that subjects will mention it spontaneously.

An intensification of the beauty and meaning of everyday things can be impressive enough to make one assume that this is how certain artists must have seen commonplace objects. Everything glows with a luminescence of its own and texture becomes three dimensional. There is a tendency to dwell on the minute, a fleck on the wall, the grain of a piece of wood. Objects develop a significance far beyond their ordinary meaning.

The "breathing" of manifestly inanimate objects is one of the more common illusions. Flowers open and close before one's eyes. Wood paneling goes in and out of focus as though the fine adjustment of a microscope were being manipulated. Misperceptions may become more complex. A face can rapidly alter its expression and appearance so that a succession of changing faces are perceived. Unconscious processes and mood states have representation in such illusory phenomena.

Pseudohallucinations are the projection of imagery, recognized as unreal, without reference to any sensory cue. This sort of misperception is more common under LSD_{25} than in true hallucinations, where the belief is held that the hallucinated object actually exists. This is so because reality contact is ordinarily not wholly lost under LSD_{25}. The projected symbolism can vary enormously; one remarkable feature is the frequency with which archetypes and scenes from previous civilizations are described. This does not imply that a racial unconscious or occult formulation need be postulated to account for prebirth experiences, detailed fantasies of ancient events, and archetypal imagery. Such phenomena may simply represent techniques that the psyche utilizes to symbolize internal conflicts and drives.

Intriguing alterations of time perception can occur. Most common is a sense of timelessness, "as though a lifetime were lived before the second hand of my watch moved." Auditory, tactile, olfactory, and gustatory aberrations are rare but have been reported. Hyperacusis is often noted. Music may be apperceived as being as remarkably transformed in meaning as viewed objects.

Major mood modulations can occur. Sometimes apprehension or anxiety is felt. In certain persons the rapid loss of ego controls may evoke panic and a painful dysphoria. For many others the state brings a serenity or an intense hyperphoria culminating in ecstatic bliss. Naturally, there is a scale of affectual changes ranging between these extremes.

The changes in thought processes are more difficult to set down. At one end of the continuum are states of contemplation approaching those described as "cosmic" or "religious" experiences. Apparently, as the ego boundaries dissolve, incomplete or complete depersonalization results. Subject-object fusion may occur and one becomes a part of the world outside without self-identity. Critical and analytic thought is in abeyance. Certain memory functions are diminished; others, for example, recall of "forgotten" incidents, may be greatly enhanced. Survival-oriented mentation is defective; instead a preoccupation with the philosophical verities comes to be of central importance.

Thinking and feeling tend to fuse into a single modality; eventually one can hardly say whether one is thinking or feeling an "idea." As a result, when the experience is a negative one, thinking can become completely disorganized with dozens of fragmentary, painful feelings tormenting the subject. Fear calls forth mental distortions and mental distortions perpetuate fear. Some of the end results of this disruptive process are autism, concretization, and paralogical and clang associations. These, of course, are reminiscent of schizophrenic thinking and account for the "model psychosis" aspects of the experience.

Except in those who willingly and gladly surrender their ego identity, the strain of "losing oneself" initiates psychological defensive maneuvers of varying magnitude. The observer can witness the major and sometimes the minor defensive pattern of a subject attempting to cope with the stressful situation. Somatization, denial, introjection, regression, compulsiveness, and other attempts to manage free anxiety become evident. For example, if the subject's major defensive position has been to project his disturbing anxieties or guilts, he may be paranoid under LSD_{25}.

Oddly enough, despite the psychotic, disorganizing elements just noted, other

subjects will describe an experience of integration, of organization, and of significance. There appear to be some persons who respond to ego dissolution with a massive reduction in tension, guilt, or conflict. A strong awareness develops that one is part of a larger, more meaningful pattern and that there is a sense of order in life. The perceptual component consists of being surrounded by dazzling light. There is an accompanying upsurge of creativity or at least an appreciation of the creative efforts of others. This is akin to the transcendental or cosmic experience, which occurs spontaneously on the rarest of occasions, and it is of some interest that this condition can be simulated with psychochemicals under proper conditions.

Insight into the knowledge that the extraordinary events taking place are chemically induced and temporary is almost never lost. Judgment is unquestionably impaired for everyday decisions. The usual frame of reference by which we measure values and the relative importance of beliefs and activities undergoes a sharp change. The pain threshold is heightened. Manual dexterity suffers and performance test scores are lower than control measurements.

Almost every subject describes a wavelike rise and fall in the intensity of the symptoms. The periodic undulations can be so marked that fluctuations between complete dissociation and almost normal contact will occur. No explanation is available for this peculiar phenomenon, but it is known that certain biochemical reactions do have cyclic activity.

The autonomic responses are minimal in comparison with the psychic changes. No subjective physiological effects may be noted. Pupillary dilation is observed with some regularity. Slight increases in blood pressure, body temperature, and tendon reflexes have been obtained. Nausea and, on isolated occasions, vomiting have occurred. Anorexia is usual during the period of drug activity.

It should be inferred from this brief description of some of the components of the LSD_{25} state that the widest variety of reactions are possible. No two experiences are ever quite alike even when monozygotic twins are given identical amounts under similar conditions. When the same subject takes a standard dose repetitively, a spectrum of responses rather than a solitary reaction pattern is obtained. The variables that modify the nature of the state are many. The most important are the personality of the subject, his current physical status, the environment, the reason for which the drug was taken, and even the personality of the observer.

LSD_{25} IN EXPERIMENTAL PSYCHIATRY

As a tool for psychological investigation the value of LSD_{25} is manifold. During the past decade neuropsychiatric research has been stimulated as much by the finding that LSD_{25} was a serotonin antagonist as by the development of the ataractic series. Without further consideration of the important neurophysiological and biochemical work that is being pursued on neuronal and enzymatic levels, the effects of LSD_{25} in man offer multiple opportunities for rewarding studies.

Quite obviously, we can scrutinize abnormal mental processes in relatively pure culture. If our interests are in perceptual deviations, autistic imagery, depersonalization, or other facets of psychotic symptomatology, these can be analyzed now under

laboratory conditions. Just as promising is the hope that "normal" behavior, communications, responsiveness to stress, character defenses, and other factors can be understood in part through the use of drugs of this type. Beyond that, perhaps something of inspirational thought and creativity will be clarified one day. The suggestion has been made that these agents might enable us to design experiments testing for the presence of extrasensory perception.

It is conceivable that psychodynamic hypotheses may be formulated in constructs that can be proved or disproved with the psychotogens. Substances like LSD_{25} could then become a part of the basic science of psychiatry.

A number of personnel in contact with psychotic patients have taken LSD_{25} and mescaline to approach the changed world in which their patients live. They claim that it is a helpful device to understand the day-to-day distortions with which their patients must cope.

The psychotomimetic state is also employed to screen drugs and procedures for use in treating the functional psychoses. This is an interesting, but not infallible, application of these agents.

Evidence is accumulating that careful use of LSD_{25} in conjunction with psychotherapy will accelerate the process of psychic rehabilitation in certain patients.[5] Resistance to the communication of repressed conflicts is reduced. The ability to handle the released guilt and anxiety is increased because of the accompanying detachment. Rapport is greatly augmented. The perceptual intensification becomes a means of projecting unconscious symbolism, and its interpretation may be of value. The corrective emotional experience of having transcended oneself is probably also therapeutic.

The most extensive application of LSD_{25} to human investigation has been in the production of a "model psychosis." A model, it should be recalled, need not faithfully reproduce the structure it is supposed to represent. Its importance in the sciences lies in its ability to teach something about the more complex original. From this viewpoint the LSD_{25} model of schizophrenia is a useful device. In certain subjects the evolution of a schizophrenic-like response can be studied in the course of a few hours.

SUMMARY

The hallucinogens are a distinct class of synthetics, plant glucosides, and alkaloids with marked psychological and lesser physiological activity. Unlike the somatochemicals, specific and predictable drug activity is difficult to delineate. The personality of the subject, the environment, and other factors can substantially modify the final response.

For millennia men have explored the psychedelic transformation for a diversity of reasons. Many sought it as a release from the cares of the day; others have hoped to approach their gods with this aid. Some have looked for fearlessness and ferocity and a few for a "saturnalia of the senses." They have been used as an ordeal, an initiation, a therapy. Now they have come under scientific scrutiny and are assisting in the understanding of deviant psychological processes. Perhaps the superlative aspects of human awareness can be systematically explored with these same agents.

BIBLIOGRAPHY

1. St. Szara, A.: Dimethyltryptamin: Its metabolism in man; relation of its psychotic effect to serotonin metabolism, Experientia *12*:441-442, 1956.
2. Garrett, E. J.: Beyond the Five Senses, New York, J. B. Lippincott Co., 1957.
3. Hoffer, A.: Epinephrine derivatives as potential schizophrenic factors, J. Clin. & Exper. Psychopath. & Quart. Rev. Psychiat. & Neurol. *18*:27–60, 1957.
4. Osmond, H.: Review of clinical effects of psychotomimetic agents, Ann. New York Acad. Sc. *66*:418–434, 1957.
5. Cohen, S., and Eisner, B. G.: Use of lysergic acid diethylamide in a psychotherapeutic setting, A.M.A. Arch. Neurol. & Psychiat. *81*:615–619, 1959.

for easy reference, practical use . . .

A GUIDE TO ANTIBIOTIC THERAPY

by Henry Welch, Ph.D.

with an introduction by
Félix Martí-Ibáñez, M.D.

"A powerful tool" in deciding antibiotic therapy, A GUIDE TO ANTIBIOTIC THERAPY is the first comprehensive and compact reference book to provide complete information on the 31 antibiotics now in use. This unusual book presents, in an easily read chart format, the following invaluable information on *each* antibiotic included: general indications, side effects, major dosage form(s), blood and urine concentrations to be anticipated, and the in vitro susceptibility of each group of important pathogenic microorganisms to the given antibiotic. All information included in A GUIDE TO ANTIBIOTIC THERAPY has been drawn from both published scientific literature and original clinical experience. It is a book no physician can afford to be without.

69 PAGES / CLOTH BOUND / $3.00

MEDICAL ENCYCLOPEDIA, INC. ▪ 30 E. 60th STREET ▪ NEW YORK 22, N. Y.

On an Armenian "Flying Carpet"*

Félix Martí-Ibáñez, M.D.

PROFESSOR AND CHAIRMAN OF THE DEPARTMENT OF THE HISTORY OF MEDICINE,
NEW YORK MEDICAL COLLEGE, FLOWER AND FIFTH AVENUE HOSPITALS;
EDITOR-IN-CHIEF OF MD MEDICAL NEWSMAGAZINE
NEW YORK, N. Y.

In his first two books on the psychological symbols buried in the knots, plaiting, colors, and images in Oriental rugs, H. M. Raphaelian, a patient and original scholar and a man of great kindness, related the enthralling tale of the secrets woven by dexterous and subtle fingers into varicolored tapestry of rugs from many parts of the world.

Now this tireless author has produced another work, as excellent and revealing as the former two, thus completing his trilogy. But while in the previous volumes he surveyed the symbols in Oriental rugs "horizontally"—in space—he here concentrates his efforts "vertically"—in time—deciphering the secrets of the rugs of a single country, his native land, that beautiful and distant Armenia, whose towns bear names as bewitching as a romantic Oriental fable. Just as by digging deep in the soul of an individual, one may find the key to all mankind, the author, by digging deep in the roots of the art of rugmaking of a single country, has found the key to that same art throughout the world.

To reach the road to universality it is not always necessary to roam first all the roads of the earth. Likewise, in fathoming a single soul or a single nation, it is possible to encounter the problems of all humanity or of all the world. Just as the miracle of love leads one to discover the perfections of all womanhood in a single woman, so the miracle of certain authors—like Cervantes and his knight-errant, so fiercely Spanish and yet so universal—can create a figure that is supreme for all time and for all the world. Such is the case with this book, which unravels many secrets of universal art, ancient and modern, merely by looking, as the author does, with eyes filled with sympathy and wonder at the colors, designs, and figures in the rugs of Armenia.

Tragic had to be the destiny of Armenia, spread as it was, like a rug of many-hued designs, across the route of conquest-hungry empires. As on a rug, the boots of invading armies from Babylon and Assyria in the past, and from Turkey in modern times, trampled over Armenia. Like Byzantium, Armenia was a gem constantly coveted by invaders, but, unlike Byzantium, Armenia had no towering walls and deep rivers to protect it, and had to fight for its historical survival not only with arms but also with souls. Armenia's longing for historical continuity was translated into its vast literary output down the centuries, especially in the fields of religion and history. It tried to win immortality through books on the grace of God and on the work of man. This longing found expression also in the develop-

---

* This article is the author's Foreword to the book *Armenian Rugs* by Harry Raphaelian (New York, Anatol Sivas Publication, 1960).

ment of the very ancient Oriental art of rugmaking, whose origin, evolution, and varieties are expertly and lucidly studied in this volume, which through its magnificent illustrations is itself like a multicolored paper rug.

Thanks to the wealth of illustrations in this book, we can see for ourselves the dazzling panorama of Armenian rugs, their history and technique, and their influence on the cognate art in other nations. We can peer into the mysteries of the Kohar and Heripsine rugs of Kabistan and the Caucasus, and may even unravel the secret of carpets made immortal through being incorporated into pictures, as, for instance, the rug in Holbein's portrait of Gyscze, which our author "diagnoses" as a Kuba rug, or the one in the portrait of Milton, here identified as a Kabistan rug decorated with a scarab motif. Rugmakers liked, the author explains, to show rugs as table runners in paintings because of the color they lent to them.

In like manner, the author explores the symbolism in Armenian rugs: the fig, a fruit symbolic of divine wisdom, fertility, and beauty; the horseshoe, a phallic symbol; the turtle, symbol of immortality; the serpent, a sexual symbol; the conventionalized bird designs, symbols of regal learning, power, and fertility. He also shows us the Chinese influence on the art of Armenian rugs, exemplified in tablets and carvings in Armenian churches.

In our trip over Armenia on this symbolic "flying carpet," we can observe the vast historic panorama of Armenian art in its numerous manifestations. The selection of plates in this book is as exhaustive as it is beautiful and original. Studying this volume, which is the transmutation of many years of research and meditation, we feel grateful to its author for sharing with us that magic world to which he holds the passkey.

The art of the Armenians, masters of rugmaking, might be compared with that of the Byzantines. In their thousand years of historic existence as an independent empire, the Byzantines turned their backs on the cruel world of enemies lurking beyond their golden walls and the azure waters of the Bosporus and took refuge in the exquisite world of miniatures, enamels, stained glass windows, and illuminated initials. Perhaps the same thing occurred with the Armenians. In the face of the historic threat that eternally hovered over them, they sought refuge in an art of eternity, precision, and fantasy like that of rugmaking.

In the noisy heart of Manhattan, the author, a dedicated and pensive man, performed an even greater miracle. Turning his back on the empire of smoke, steel, and concrete around him, he retreated into the fine and subtle world of the symbols in his rugs. For that alone he deserves our warmest admiration and affection.

Diseases of the Chest including the Heart. EDITED BY J. ARTHUR MYERS, PH.D., M.D. Springfield, Ill., Charles C Thomas, 1959. Pp. 1015. Price $34.50.

Thirty-four contributors discuss all aspects of chest and heart diseases in this valuable book. The book is a generous 1015 pages, 7¼ by 10¼ inches in size, and it weighs more than 5 pounds—although even with these dimensions and the excellence of content and format, it is greatly overpriced at $34.50.

Among the many outstanding contributions are a description of the various segments of each pulmonary lobe that can be removed without sacrificing normal segments, indications for chest surgery, factors in management of all types of pneumonia, treatment of chest injuries, heart operations, repair of injuries to the heart and great vessels.

The contributors to the book are all authorities in their particular area of this broad subject, and the book is, as a result, an outstanding volume. It is unfortunate that the price of the book may prevent its getting the wide readership it deserves.

William Harvey and the Circulation of the Blood. 16 mm. color film, sound, 1957. Sponsored by the Wellcome Trustees for the Royal College of Physicians of London, and produced by the Wellcome Film Unit, Burroughs Wellcome and Company. Distribution (U.S.A.): Burroughs Wellcome Laboratories, Scarsdale Road, Tuckahoe 7, N. Y.: American Medical Association Film Library, 535 North Dearborn Street, Chicago, Ill. Running time: 35 minutes.

This excellent film, prepared in honor of the tercentenary of William Harvey's death in 1657, is a skillful remake of an earlier film sponsored by the Royal College of Physicians in 1928 on the tercentenary of the publication of Harvey's monumental work *De motu cordis*. The current film has been updated by the addition of a sound track, color, and animation.

The distinguished investigator, Sir Henry H. Dale, scientific consultant for the film, delivers a brief introductory comment and also acts as commentator. Harvey's life is outlined, using old paintings and classic iconography as background, and then a description is given of the earlier contributions on the study of the circulation by Harvey's predecessors, including Galen, Vesalius, and Servetus. Next are illustrated —graphically and in detail—some of Harvey's most important experiments on the circulation, done without instruments but with a lot of logic and common sense. A running commentary by Dr. Leonard Goodwin, using passages from *De motu cordis* and speaking as Harvey, serves as descriptive narration of the film.

The photography of this film is excellent and the sequences are well integrated and effective. The film is highly recommended as an excellent portrayal of Harvey's work on the circulation of the blood, perhaps the most significant contribution ever made to medical science.

SHIGELLOSIS TREATMENT. A total of 45 patients with significant diarrhea caused by Shigella organisms were treated with furazolidone (Furoxone, Eaton) in a controlled study in Egypt (AM&CT 7:17, 1960). All patients were free of diarrhea five days after treatment was begun; stools were negative for Shigella in all but 1 patient within four days; no toxic effects were noted.

RENAL ARTERY GRAFTS. In 21 of 28 patients with renal hypertension, normal blood pressure has been restored by substitution of synthetic Dacron grafts for the occlusive kidney lesion, according to a report at the recent Southern Surgical Association meeting. The grafts have remained intact up to three years. One third of the 39 lesions were bilateral; 29 were in the proximal third of the renal arteries.

TREATMENT OF GAS AND BLOATING. Methyl polysiloxane (Mylicon, The Stuart Co., Pasadena, Calif.) gave good or excellent results in 84 of 117 patients with excessive intestinal gas and bloating, who had not obtained relief on previous therapies (Am. Pract. & Digest Treat. 11: 52-57, 1960). The drug was given in 40 mg. tablets after meals and at bedtime. The therapeutic action of the agent results from its physicochemical properties, which change the surface tension of gas bubbles in the gastrointestinal tract.

AMMONIA ANTI-INTOXICANT. Indicated for patients with ammonia intoxication due to hepatic failure is arginine hydrochloride and sodium glutamate (Modumate, Abbott), administered by intravenous infusion. The drug reduces blood levels of ammonia without correcting the underlying causes of hepatic coma. The drug is not recommended for hepatic disorders in which blood ammonia levels are relatively normal.

HYALURONIDASE IN ACUTE MYOCARDIAL INFARCTION. Intravenous hyaluronidase produced rapid improvement in the ST segment of patients with acute myocardial infarction (Am. J. Cardiol 4:275, 1959). The beneficial effect was attributed to reduction of edema in the damaged area, with consequent lessening of injury to the myocardial fibers during the critical first stage after acute coronary occlusion.

ORAL ERYTHROMYCIN PROPIONATE. Propionyl erythromycin (Ilosone, Lilly) administered orally was shown to produce higher and longer sustained blood levels than erythromycin base (AM&CT 7:193, 1960). Of 125 cases, representing a cross-section of infective conditions commonly encountered in general and geriatric practice, satisfactory clinical response was obtained in 117. The incidence of side reactions was low (4.8 per cent).

IMPROVED HEMATINIC. Now available is an improved formula (Heptuna Plus Capsules, Roerig) for treatment of microcytic and macrocytic nutritional anemias. Advantages of the new formula include: iron source changed to ferrous fumarate and amount of elemental iron increased; change in form of vitamin B_{12}; addition of intrinsic factor; increase in folic acid, calcium pantothenate, niacinamide, and vitamins B_1, B_6, and C.

RESPIRATORY CENTER DURING PREGNANCY. Evidence that the sensitivity of the respiratory center is increased during pregnancy was reported at the recent meeting of the Western Society for Clinical Research. Significant differences with respect to carbon dioxide tension in subjects during and after pregnancy were demonstrated. The increased sensitivity was associated with true hyperventilation and appears to occur shortly after conception (within hours to 10 days). The mechanism underlying the change is not yet understood.

SAMARIUM-153 RADIOGRAMS. Medical radiograms of diagnostic quality comparable to conventional roentgenograms are being experimentally produced at the General Motors Research Laboratories (Warren, Mich.) by a newly developed low-energy, short-lived radioisotope—samarium-153. The new technique may prove valuable wherever standard roentgenography would be impossible—in the field, in emergency or disaster situations, and in remote jungle areas. The technique would supplement conventional roentgenography, not supplant it.

TRANSPORTABLE OXYGEN UNIT. A new oxygen unit (marketed as AerOxygen by Aerojet General Corp., Azusa, Calif.) produces an unlimited supply of oxygen from the atmosphere: the device filters contaminants out of air, extracts oxygen, and delivers the gas at approximately 5 lb./sq. inch pressure in less than one minute after activation. The present model is about 2 feet square, weighs 150 lb., and operates on ordinary house current; later models will be gasoline or battery powered and available in various shapes and sizes.

QUARTERLY REVIEW OF OPHTHALMOLOGY

(For the Medical Profession)

Editor-in-Chief: CONRAD BERENS, M.D., *New York, N. Y.*
Executive Editor: ARNOLD S. BREAKEY, M.D., *New York, N. Y.*

Associate Editors:
GEORGE E. ARRINGTON, JR., M.D., *Richmond, Va.*
GEORGE Z. CARTER, M.D., *New York, N. Y.*
DAHAR CURY, M.D., *Huntington Park, Calif.*
G. PETER HALBERG, M.D., *New York, N. Y.*

Associates for Reviews:
RICHARD M. DENNIS, M.D., *Waterville, Me.*
THOMAS P. KEARNS, M.D., *Rochester, Minn.*
CARL KUPFER, M.D., *Boston, Mass.*
RALPH Z. LEVENE, M.D., *New York, N. Y.*
FRANK D. McAULEY, M.D., *Dublin, Ireland*
CLEMENT McCULLOCH, M.D., *Toronto, Ontario*
GARRETT SULLIVAN, M.D., *Boston, Mass.*

NATIONAL EDITORIAL BOARD

WALTER S. ATKINSON, M.D.
Watertown, N. Y.
ROBERT E. BANNON, D.O.S.
Southbridge, Mass.
WILLIAM L. BENEDICT, M.D.
Rochester, Minn.
EUGENE M. BLAKE, M.D.
Yale University
HENRY N. BRONK, M.D.
Pittsburgh, Pa.
JOHN W. BURKE, M.D.
Washington, D. C.
DAVID G. COGAN, M.D.
Harvard University
FREDERICK C. CORDES, M.D.
University of California
ALFRED COWAN, M.D.
University of Pennsylvania
C. L. CROUCH
New York, N. Y.
PERCE DeLONG, M.D.
University of Pennsylvania
EDWIN B. DUNPHY, M.D.
Harvard University
F. BRUCE FRALICK, M.D.
University of Michigan
GLEN FRY, O.D.
Ohio University
EVERETT L. GOAR, M.D.
Houston, Texas
JAMES N. GREEAR, M.D.
Reno, Nev.
JACK S. GUYTON, M.D.
Detroit, Mich.
PARKER HEATH, M.D.
Sullivan Harbor, Me.
S. RODMAN IRVINE, M.D.
University of Southern California
ARLINGTON C. KRAUSE, M.D.
Chicago, Ill.
MICHEL LOUTFALLAH, M.D.
Santa Barbara, Calif.
DONALD J. LYLE, M.D.
University of Cincinnati
JULIUS NEUMUELLER, O.D.
Haddonfield, N. J.
CECIL S. O'BRIEN, M.D.
Tucson, Arizona
BRITTAIN F. PAYNE, M.D.
New York University Medical College
OGDEN D. PINKERTON, M.D.
Honolulu, T. H.
ALGERNON B. REESE, M.D.
Columbia University
C. WILBUR RUCKER, M.D.
Mayo Foundation
ALBERT D. RUEDEMANN, M.D.
Wayne University
G. VICTOR SIMPSON, M.D.
Washington, D. C.
K. B. STODDARD, PH.D.
University of California
GEORGIANA DVORAK-THEOBALD, M.D.
Chicago, Ill.
PHILLIPS THYGESON, M.D.
San Jose, Calif.
DERRICK VAIL, M.D.
Northwestern University
ROBERT T. WONG, M.D.
Honolulu, T. H.
JOSHUA ZUCKERMAN, M.D.
New York University

INTERNATIONAL EDITORIAL BOARD

MARC AMSLER, M.D.
Universitates-Augenklinik
Zurich, Switzerland

J. RINGLAND ANDERSON, M.D.
Melbourne, Australia

RAUL ARGANARAZ, M.D.
Buenos Aires, Argentina

HERMINIO ARRUGA, M.D.
Barcelona, Spain

L. E. BARRERE, M.D.
Lima, Peru

ALBERTO VAZQUEZ BARRIERE, M.D.
Montevideo, Uruguay

RODRIGUEZ BARRIOS, M.D.
Montevideo, Uruguay

M. SOBHY BEY, M.D.
Cairo, Egypt

GIAMBATTISTA BIETTI, M.D.
Rome, Italy

LUIS SANCHEZ BULNES, M.D.
Mexico, D. F.

HOWARD COVERDALE, M.D.
Auckland, New Zealand

SIR STEWART DUKE-ELDER, M.D.
London, England

STEPHEN DE GROSZ, M.D.
Budapest, Hungary

A. HAGEDOORN
Universiteit van Amsterdam
Holland

EDWARD HARTMANN, M.D.
Paris, France

RAFAEL IRRIBARREN, M.D.
Buenos Aires, Argentina

ALEXANDER JOKL, M.D.
Johannesburg, South Africa

KARL LINDNER, M.D.
Vienna, Austria

T. H. LUO, M.D.
Peiping, China

JORGE MALBRAN, M.D.
Buenos Aires, Argentina

EDGARDO MANZITTI, M.D.
Buenos Aires, Argentina

HENRIQUE MOUTINHO, M.D.
Lisbon, Portugal

J. V. V. NICHOLLS, M.D.
McGill University Medical School
Montreal

R. PACHECO-LUNA, M.D.
Guatemala City, Guatemala

JESUS RHODE, M.D.
Caracas, Venezuela

L. B. SOMERVILLE-LARGE, M.D.
Dublin, Ireland

TOMAS R. YANEZ, M.D.
University of Havana

FOREWORD: A New Policy

The objective of the QUARTERLY REVIEW OF OPHTHALMOLOGY is to bring together in one publication a concise record of current happenings, both national and international, in this field. Selection and editing of material are designed to prove informative to *the entire medical profession* as well as to ophthalmologists. Manuscripts for the QUARTERLY REVIEW OF OPHTHALMOLOGY should be submitted to Dr. Arnold S. Breakey, Ophthalmological Foundation, 111 East 59th St., New York, N. Y.

Three Physiologists: Their Impact on Ophthalmology

Young, Müller, and Helmholtz

George E. Arrington, Jr., M.D.

RICHMOND, VA.

The nineteenth century is characterized as a period of rapid and dramatic changes in technology that resulted in both industrial and scientific revolutions. Of equal significance to the technical progress was a shifting of emphasis among natural scientists concerning explanations of the problem of ultimate reality, of the sources and theory of cognition (epistemology), and of the limits of our understanding of nature. These problems are particularly pertinent in ophthalmological thought, which deals so directly with perception of the highest order—vision.

Thomas Young (1773–1829), the British genius, was known for his brilliance and originality in many diverse fields, including ancient and modern languages, physics, optics, archeology, and physiology. Young studied medicine in London, Cambridge, and Edinburgh as well as Göttingen on the European continent, beginning his practice in London in 1799; however, his active practice was short-lived, for he accepted the chair of physics at the Royal Institution in 1801. Young was elected a fellow of the Royal Society in 1794 and in 1803 resigned as professor of physics and became foreign secretary to the Royal Society.

Fortunately for ophthalmology, Young turned his great intellect to optics and to the physical aspects of the visual mechanism. Thus he studied and made important original contributions to the knowledge of accommodation. Although he incorrectly believed the lens itself to be a muscular structure, he was basically correct in assuming that changes in this structure were responsible for accommodation. His writings included *The Accommodation of the Eye* (1802) and *On the Mechanism of the Eye* (1801). Young studied and correctly described astigmatism by measuring various diameters of his own cornea.

It was Young who "... developed the knowledge of visual fields quite thoroughly and established the difference of character of the central and peripheral vision, especially as they relate to color."[2]

As a physicist, looking at visual function, Young approached color vision from the Newtonian concept of three primary colors, which he adopted but modified. It was Young, the physicist, who, by experiment with the interference of light, established in 1801 Huygens' undulatory theory of light (wave theory), earlier alluded to by Leonardo da Vinci. In assuming this theory, as Whitehead pointed

---

EDITOR'S NOTE: This is the continuation of a series of articles on the contributions to ophthalmology of great men in history. Dr. Arrington is eminently qualified for the task for he has made a prolonged study of the subject and has written *A History of Ophthalmology* (New York, MD Publications, Inc., 1959).

out, there is implied that there must be something to undulate—matter or ether.

Thus Young is established as the first great thinker of the nineteenth century to relate physics and ocular function, and here we have the beginnings of modern physiological optics, which was brought into full development later in the works of Donders and Helmholtz. One also perceives the germ of scientific materialism in Young's distinction of energy as an exact physical quantity,[3] which helped to pave the way for Helmholtz's law of the conservation of energy. Thus Young represents a turning point in the history of ophthalmology in his early attempts to establish visual function on a sound mathematical and physical basis in tune with the general tenor of his age.

Johannes Müller (1801–1858) has justly been called the "father of modern physiology." His claim to this distinction rests on his discovery of the experimentally proved fact that specific nerves, when stimulated by whatever various external means, always give rise to specific sensations—the law of the specific energy of the nerves. This principle was first described in relation to pressure phosphenes in the eye, which cause light sensation on pressure and electrical, thermal, and pharmocogenic stimuli. But "energy," in the Müllerian as in the Aristotelian sense of *energia* or *entelechia*, indicates a completely actualized potential rather than a force, as the term "energy" is used in modern physics. Thus, as Riese contended, ". . . One cannot escape the conclusion that in the final analysis the law of the specific energies of the nerves rested on a metaphysical rather than an anatomical or physiological argument."[4]

Müller never completely forsook his early vitalism, which was favored by many naturalists of his time. Can our own generation forget that life is unique, its manifestations indeterminable by analysis of the component parts, and is vision not a particular of life?

Müller came from humble parentage, but he showed his intellectual promise early. He intended at first to enter theology, but he turned to medicine, being graduated from Bonn in 1822. Inspired by Rudolphi in Berlin, where he studied anatomy for a year and a half, he determined to teach rather than practice medicine. Returning to Bonn, he became *Privatdocent* and later professor of anatomy and physiology. When Rudolphi died, Müller succeeded him at the University of Berlin as professor of anatomy, physiology, and pathology, which post he held for 25 years, until his death. It was in Berlin that Müller gained renown as a teacher and original thinker in these and other fields, attracting many students among whom were Helmholtz, Emil Du Bois-Reymond, Brücke, Virchow, Schwann, Remak, and Henle, each destined for personal greatness. Müller was highly respected, being called by both students and faculty "The Olympean."

However, his own famous pupil, Helmholtz, became an advocate of the "physical school," which opposed the vitalists, and as we shall see, he failed to grasp the soundness of many views held by Müller.

The translation of Müller's physiology text, *Handbuch der Physiologie des Menschen* (1833–1840) into *Elements of Physiology* (1843) omits a great deal, including the significant passage containing his views on the problem of the inverted image.[5] In this textbook he contended that sensation is knowledge of the conditions of the

sense nerves, each in terms of its own quality. Thus, according to Müller, it is our own inner world that we sense (or know) in terms of our own potential qualities, but we do not sense the nerves themselves. Helmholtz called these qualities "innate," though he disputed their existence.

The principle of specific energy implies also specific irritability, that is, that certain sensory nerves respond most sensitively to certain specific external agents. For example, the retina and optic nerve react most strongly to physical light energy, the organ of Corti and the acoustic nerve most strongly to vibrations of air, etc. However, these same nerves can react to a much lesser degree to other stimulating agents, such as pressure and electricity, but always with perception in terms of the specific energy of the nerve being affected.

Müller also wrote a work dealing with the psychological aspect of vision, i.e., visual hallucinations, fantasies, and illusions, entitled *Phantastische Gesichtserscheinungen* (1826) (*On Fantastic Visual Phenomena*). The same year saw the appearance of his *Zur Vergleichenden Physiologie des Gesichtssinnes*. He also wrote more than two hundred articles and monographs, and in 1834 he established his journal *Archiv für Anatomie und Physiologie* ("Müller's Archiv").

The influence of Müller on ophthalmology is as strong as his influence on general human physiology, and no serious student of ophthalmology can afford to miss contact with the ideas of this great genius.

Hermann von Helmholtz (1821–1894), professor of physiology and pathology at the University of Königsberg (1849), was without question the man most widely associated with scientific thought in the nineteenth century. Helmholtz was a 26-year-old army surgeon when he published his treatise on *Conservation of Energy* (*Über die Erhaltung der Kraft*) (1847). This immediately established him as a scientist of the highest caliber. Five years later, while studying the lens in accommodation, he devised his "*eye mirror*" (*Augenspiegel*) and published a description of this and other works in his *Handbuch der Physiologischen Optik* (Leipzig, 1856–1866). This instrument rapidly gained wide acceptance and use in the hands of ophthalmologists, such as von Graefe, Saemisch, Sweigger, and Sichel in Germany, Albutt and Hutchinson in England, and Gahezowski and Bouchut in France.[6] Clearly this development changed the character of the specialty more than any other single event. Ophthalmology gained stature as an independent discipline and lost forever its status as a surgical subspecialty. Medical ophthalmology reached a diagnostic acumen never before known, and the nature of glaucoma, diseases of the interior of the eye, and refractive characteristics became clear for the first time as a result of the ophthalmoscope. In addition, Helmholtz invented the ophthalmometer in 1854.

However, his appointment in 1871 to the chair of physics at the University of Berlin attested to the fact that Helmholtz was primarily a physicist and a mathematician as well as an experimenter in human physiology. He also demonstrated deep interest in the philosophical implications of his discoveries. His address entitled "*Das Denken in der Medicin*" (1877) ("Thought in Medicine"), delivered when he was 56 years old, is a classic in the history of medicine; this lecture discussed the discovery of natural laws and compared it with "the highest performances of artistic perception." Hemholtz considered vision from the empirical stand-

point, assuming that we learn to see, that space is derived from proprioception, and that color vision is trichromatic with separate physical receptors for each of three primary wave lengths (Young-Helmholtz theory).[7] Helmholtz thus denied Kant's assumption of space as an a priori concept, which he discussed in one of his popular lectures on scientific subjects.[8] Sensations are "signs" that we learn to decipher ". . . a language given us with our organization by which external objects discourse to us."

It was Helmholtz's intention to preserve philosophy for science by reorganizing it along empirical lines. In discussing Hegel's "philosophy of identity," Helmholtz granted the possibility of constructing results of science a priori provided these sciences "grow out of out moral nature such as theology, law, politics, history, etc. but he denied it in the field of natural science."[3]

This dispute has direct bearing on ophthalmology, which seeks to comprehend not only the mechanics of vision but the essence of seeing man as well. Thus we recognize that the "nineteenth century empiricists often failed to see the strength of bearings of the view that experience does not lead us directly to things as they are, but is only a process by which the appearance of things arises in our minds, and that therefore the picture of nature we construct is partly determined *a priori* by the structure of our minds, as also is the fact that we have experiences at all."[3] For Helmholtz, the solution of the problem of reality lay in understanding mass and force. Thus his principle of the conservation of energy supported scientific materialism and its allies, mechanism and determinism. These developments are understandable, appearing as they did in the midst of nineteenth-century success of the atomic theory, theories of electricity and magnetism, and chemistry of organic and inorganic compounds; however, the perspective of years gives us the advantage of measuring the achievements of these great thinkers in more objective terms. Their contributions remain undimmed, but science has mellowed considerably, and we see that certain aspects of the problems of perception and vision remain unfathomed by science—something will always remain to be understood no matter how far we advance. The wisdom of Du Bois-Reymond attains new validity with the proof of the years—*ignorabimus*.

BIBLIOGRAPHY

1. Whitehead, A. N.: An Introduction to Science.
2. Arrington, G. E., Jr.: A History of Ophthalmology, New York, MD Publications, Inc., 1959, pp. 100, 112.
3. Dampier, Sir W. C.: A History of Science, Cambridge, Cambridge University Press, 1958, pp. 226, 292, 294.
4. Riese, W.: A History of Neurology, New York, MD Publications, Inc., 1959, p. 123.
5. Riese, W., and Arrington, G. E.: Johannes Müller on the inverted image. A new and unabridged translation, Am. J. Ophth. *47*:185.
6. Chance, B.: Sir Clifford Albutt, apostle of medical ophthalmoscopy, Arch. Ophth. *17*:819–858, 1937.
7. Linksz, A.: Physiology of the Eye, vol. 2, p. 303 et seq.
8. Helmholtz, H.: On the Relation of Natural Science to General Science, Popular Lectures on Scientific Subjects, London, Longmans Green & Co., 1873, p. 1.
9. Young, T.: An Introduction to Medical Literature Including A System of Practical Nosology, London, 1813.

10. Young, T.: Miscellaneous Works, collected by G. Peacock, London, 1855, 3 vol.
11. Wood, A., and Oldham, F.: Young, Thomas: Natural Philosopher (1773–1829), Cambridge, Cambridge University Press, 1954.
12. Chance, B.: Johannes Müller, a sketch of his life and ophthalmologic works, Arch. Ophth. 32:395.
13. Haberling, W.: Johannes Müller, Das Leben des rheinischen naturforschers, Leipzig, 1924.
14. Müller, M.: Über die Philosophichen Anschauungen des Naturforschers Johannes Müller, Leipzig, Barth, 1927.
15. M'Kendrick, J. G.: Hermann Ludwig Ferdinand von Helmholtz, London, Longmans, Green & Co., 1899.
16. Kolnigsberger, L.: Hermann von Helmholtz, translated from the German by F. A. Welby, London, Oxford University Press, 1906.
17. Helmholtz, H. von: On the Sensations of Tone as a Physiological Basis for the Theory of Music, translated from the German by Alexander J. Ellis, Peter Smith, 1948.
18. Southall, J. P. C., editor: Helmholtz's Treatise on Physiological Optics, Optical Society of America, 1924–1925.
19. Engleman: Gedächtnissrede auf Hermann von Helmholtz, 1894.
20. Helmholtz, G. von: Beschreibung eines Augen-spiegels zur Untersuchung der Netzhaut im lebenden Auge. A Forstner'sche, Verlagsbuchhandlung, Berlin, 1851; K. Sudhoff Klassiker der Medizin, J. A. Barth, Leipzig, 1910; English translation by T. H. Shastid, Chicago, Cleveland Press, 1916.
21. Helmholtz, H. von: Schriften zur Erkenntnistheorie, Berlin, J. Springer, 1921.

---

antibiotica, inc., is pleased to present the new

antibiotics annual 1959-60

edited by Henry Welch, Ph.D.
and Félix Martí-Ibáñez, M.D.

An indispensable volume for every physician, research worker, and educator, the new *Annual* contains the complete proceedings of the Seventh Annual Symposium on Antibiotics, held in Washington, D. C., November 4, 5, and 6, 1959. This unique book features 160 papers covering the latest theories and discoveries in the field of antibiotics. A few of the new antibiotics covered include: potassium alpha-phenoxyethyl penicillin, a new synthetic penicillin; the new antibiotic colistin; aspartocin; fervenulin, a new crystalline antibiotic; and many others of importance. In addition, there is comprehensive coverage of the standard antibiotics and such special articles as "The Great Historical Challenge in Medicine" by Félix Martí-Ibáñez, M.D., and "The Challenge of New Drugs to the Clinical Investigator" by Maxwell Finland, M.D. Illustrations, charts, and a comprehensive index are included.

1034 Pages / Cloth Bound / $15.00

antibiotica, Inc. / 30 E. 60th Street, New York 22, New York

PREVENTIVE OPHTHALMOLOGY

UNDIAGNOSED GLAUCOMA

The urgent need for preventive orientation of ophthalmology was recently emphasized by a number of surveys that demonstrated a shockingly high incidence of undiagnosed glaucoma in the United States population. Horsley and co-workers recently found, in a large random sampling of visitors to a medical center (none of them had ophthalmic complaints), that 4 per cent had undiagnosed chronic glaucoma.

In this country, Berens and his co-workers have stated for years the need for large screening projects and the gradual education of physicians and the public to pay attention to this important health factor.

A small, inexpensive, handy instrument—the ophthalmic hypertension indicator—permits the medical practitioner to include routine checking of the intraocular pressure in his physical examination. Once versed in the handling of the instrument, the practitioner will not hesitate to use it routinely. Some physicians have already learned how to use the Schiøtz tonometer, the instrument used by the majority of ophthalmologists throughout the world for checking the intraocular pressure.

If we bear in mind that approximately 4 of every 100 persons in the United States have undiagnosed glaucoma—a severe, insidiously blinding disease—we will realize that there is no justification for an easygoing attitude. It also seems imperative that a check of intraocular pressure be made part of every routine medical examination. Half-yearly dental examination is an accepted routine. Examination for glaucoma on a yearly basis for all persons older than 35 should become just as routine.

READING PROBLEMS AND EYE MUSCLE BALANCE

Better eye examinations have produced an awareness on the part of the medical practitioner and the public of ophthalmic problems in school age children.

Unfortunately, many ophthalmologists are not yet convinced of the important role that very small errors in the ocular muscle balance can play in reading disabilities. All too often, children with a reading disability are dismissed as a "psychiatric problem." Small refractive errors also are treated by many ophthalmologists as too insignificant to be bothered with. Many physicians are all too willing to give in to the parents' wish: "I hope that you do not have to give Johnny glasses." If certain types of small astigmatic errors are not corrected, great strain can be put on the child, which might be the root of reading problems.

ORTHOPTICS, PLEOPTICS, AND AMBLYOPIA

In preventive ophthalmic care, especially of the school age group, a thorough examination and evaluation by a certified orthoptic technician is of great importance. Orthoptic technicians are ancillary workers who are attached to ophthalmological offices or clinics. They receive a rigid course of training, practical and theoretical,

and their attention is acutely focused on the finest details of malfunction of the ocular muscle balance.

Recent work by a number of investigators has pointed out new ways of handling the majority of amblyopia ex anopsia (so-called "lazy" eye) cases. It seems to be safe to state that many of these cases are due to excentric fixation in the partially blind, "lazy" eye. The new treatment system—pleoptics—permits active treatment and re-education of "lazy" eyes. An interesting aspect of the new treatment is that, instead of patching the good eye and forcing the patient to use the bad eye, in pleoptics we patch the bad eye and try to break the erroneous habit of excentric fixation. Since the poor eye is covered between training sessions, the young patients show very good cooperation in this form of treatment.

EYE EXAMINATION OF INFANTS

Preventive ophthalmology should start at the earliest age. It is commonly overlooked by the public and also by some practitioners that ophthalmology is an objective discipline and that many factors concerning the organ of vision can be checked and corrected without the active cooperation of the patient. It is a widespread belief of the general public that the ophthalmic examination is based almost exclusively on subjective responses. This is obviously not so. Visual acuity of infants can be tested with small sugar granules (using confectioners' colored sugar granules), to mention one of the numerous procedures and observations that can be made objectively. Corrective glasses that will prevent turn of the eyes (strabismus) and even eventual later surgery can be given to a child as young as 17 months. Routine eye examination of infants by an ophthalmologist at the earliest opportunity is actively urged by the writer.

Routine eye examinations for infants, school age children, and adults should be made twice yearly, irregardless of whether or not there is any disturbance of vision or ocular discomfort. Children and adults alike are often not aware of the fact that the vision is impaired in one eye. Slight visual field changes often go unnoticed. To encourage the patient to seek ophthalmic help only when a disturbance is present in the form of visual acuity loss or of pain in or around the eye is an outmoded concept, which is untenable under modern circumstances and has proved much too costly both for the persons involved and for the community, which has to care for the blind.

G. Peter Halberg, M.D.
New York, N. Y.

ABSTRACTS

OPHTHALMOLOGY PER SE

16. *The Problem of Unilateral Amblyopia, an Editorial.* J. C. LOCKE. Canad. M.A.J. *81*:570–571, Oct. 1, 1959.

Unilateral amblyopia is a lasting disability in 3 to 6 per cent of afflicted persons. The problem may be attacked along four lines: increased awareness of the problem by the general public, greater appreciation of the magnitude of the disability by the medical profession, preschool screening programs, and continuing application of the latest methods of treatment. 12 references.—*Clement McCulloch, M.D.*

17. *The Diagnosis and Treatment of Simple Glaucoma.* SIR STEWART DUKE-ELDER. Canad. M.A.J. *82*:293–297, 1960.

The diagnosis of simple glaucoma depends on three factors: the tension of the eye, the appearance of the disc, and the visual fields. Of these, the most important are the visual fields. The underlying cause is essentially a vasosclerosis. If the sclerosis is in the anterior segment of the eye, there will be an early rise in tension. There is a central mechanism controlling ocular tension, and thus the early disturbance of ocular tension in glaucoma may be due to a disturbance of this central mechanism.

One reading of the tonometer is of little value. The tension should be taken throughout the day. Diagnostic tests include the water-drinking test, tonography, and the bulbar pressure test. Tonography is open to criticism in that the coefficient of elasticity of the sclera may vary with the ocular pressure. The pressure in episcleral veins varies when the tonometer is placed on the eye. Pressure on the intrascleral veins may vary considerably from case to case. Finally, the rise in ocular pressure during tonography probably decreases the formation of aqueous humor. For these reasons the bulbar pressure test of Blaxter is preferred.

To follow the appearance of the discs, it is necessary to photograph or draw them.

Concerning treatment, operation should not be performed unless function is becoming impaired, as evidenced by the visual fields. 13 references.—*Clement McCulloch, M.D.*

18. *Surgical Rotation of the Eyeball.* R. RODRÍGUEZ BARRIOS, E. MARTÍNEZ RECALDE, CARLOS MENDILAHARZU, AND CÉLICA MENDILAHARZU. Brit. J. Ophth. *43*:584–595, 1959.

The authors have performed surgical rotation of the eyeball for 5 patients who had detachment of the retina. Their purpose in carrying out such an operation was to convert a superior retinal detachment into a more inferior one and thereby enlist the aid of gravity.

The eyes were rotated approximately 90 degrees, by being either intorted or

extorted. All the rectus muscles were severed and the oblique muscle that prevented the torsional movement likewise was severed. The globes were rotated approximately 90 degrees and the muscles were reattached to the adjacent stumps. In other words, the lateral rectus muscle would be reattached to the stump of the superior rectus muscle, so that the globe was thereby rotated 90 degrees. The authors found that if the globe was rotated more than 90 degrees, the central retinal artery collapsed and ischemia of the optic disk appeared. It was also important to exercise care so as not to disturb the vortex veins. After this rotation of the globe, surgical treatment of the detached retina was carried out.

All 5 patients followed "a rather difficult postoperative course." The authors write that no conclusions as to the efficacy of the surgical treatment can be made on the basis of such a small number of patients, but some interesting observations were made on the visual phenomena experienced by patients with rotated eyeballs.

The patients saw letters on the E chart as if they were rotated 90 degrees opposite to the actual rotation of the globe. When the patient was asked to place a ruler parallel to one the examiner showed him, it would be placed in a position almost 90 degrees opposite. Because of the visual confusion, the patients were unable to walk with the operated eye as a guide. Fusion on the synoptophore was accomplished when the proper slide was rotated 90 degrees. The visual fields, as would be expected, also were rotated, and the widest part of the field was found to be inferior if the lateral rectus muscle had been reattached to the inferior rectus muscle. The ocular movements were interesting. It was found that the voluntary movements of the eyes were normal, that is, when the patient was asked to move his operated eye to the right, this maneuver could be carried out. However, the following movements of the eye were off 90 degrees: If an object was placed in the lower field of the operated eye and the patient was asked to look toward it, the eye would move temporally. The optokinetic nystagmus also was off 90 degrees with respect to the drum lines.

After a few months, when the detached retina was successfully reapposed, the eyeball was again rotated to its original position. The authors point out, however, that this was accomplished in only 2 patients.—*Thomas P. Kearns, M.D.*

19. *Studies on the Living Cornea in Vitro. 1. Methods and Physiological Measurement.* A. DONN, D. M. MAURICE, AND N. B. MILLS. A.M.A. Arch. Ophth. *62*:741–747, 1959.

Using a technique developed by Ussing, an electric potential between 15 and 40 mv. is recorded across the excised rabbit cornea in vitro. This potential is dependent on the epithelium and disappears when the epithelium is removed.—*Carl Kupfer, M.D.*

20. *Studies on the Living Cornea in Vitro. 2. The Active Transport of Sodium Across the Epithelium.* A. DONN, D. M. MAURICE, AND N. B. MILLS. A.M.A. Arch. Ophth. *62*:748–757, 1959.

Utilizing the technique described previously, the movement of radioactive sodium

across the epithelium in the excised rabbit cornea is measured. There appears to be a net transfer of sodium across the epithelium into the stroma. This net flux of sodium is almost equivalent to the electric current necessary to neutralize the electric potential that exists across the cornea.—*Carl Kupfer, M.D.*

21. *Studies on Intraocular Effects of the Orbital Parasympathetic Pathway. III. Effect of Steady State Dynamics.* M. F. ARMALY. A.M.A. Arch. Ophth. *62*:817–827, 1959.

Using his technique of electric stimulation of the parasympathetic nerves synapsing in the ciliary ganglion of the cat, Armaly found that the outflow facility appears to increase with electrive stimulation of this nervous pathway, as measured utilizing constant pressure and constant rate perfusion techniques. The increased aqueous outflow is considered to be due to the contraction of the ciliary musculature. Of added interest is the observation that stimulation of the parasympathetic pathways brought about an increase in inflow rate. This suggests that inflow and outflow may change simultaneously, thus regulating the level of the intraocular pressure.—*Carl Kupfer, M.D.*

22. *Congenital Dyslexia: A Problem in Etiology.* JOHN V. V. NICHOLLS. Canad. M.A.J. *82*:575–579, March 12, 1960.

Three out of 4 children can learn to read with ease. The remainder are now classified as retarded, but 3 out of 4 of these can learn to read well if presented with modifications of current teaching methods. The remaining group show the effects of auditory defects, cerebral damage, or emotional disturbances. Ocular defects are only a contributing factor and do not initiate the difficulty. Early recognition is essential and a varied and elastic educational approach an absolute necessity.—*Clement McCulloch, M.D.*

23. *Degeneratio Punctata Albescens.* LOUIS MEYERSON. Brit. J. Ophth. *43*:635–637, 1959.

The author attributes the first report of this disorder to Mooren in 1882 and notes that about 50 cases have been reported since then.

Night blindness is present in degeneratio punctata albescens and sometimes is more a retardation of adaptation to dark than an absence of such adaptation. Peripheral contraction of the visual fields, most marked in dim light, is present in more than half of the cases. Central vision is good and remains so, since there is no progression of visual loss. The fundus is peppered with discrete white dots lying deep to the retinal vessels. Primary pigmentary degeneration of the retina in other members of the family is common.

The author, writing from Johannesburg, South Africa, reports an example of this retinal disease in a 48-year-old woman of Portuguese descent. Although the other members of the family were not examined, this same disorder was thought to be present in 7 other members of the patient's family, representing three generations.—*Thomas P. Kearns, M.D.*

24. *Conjunctival Amyloidosis.* S. P. MATHUR, AND B. P. MATHUR. Brit. J. Ophth. *43*:765–766, 1959.

Two cases of primary amyloidosis of the conjunctiva are reported. The lesions presented as painless tumors of the conjunctiva overlying the tarsal plates. In 1 patient both the upper and lower lids of each eye were involved; in the other patient only the upper lid of one eye was involved.

Both patients were from Rajasthan, India, where nearly 80 per cent of the population is affected by trachoma. The authors believe that primary amyloidosis of the conjunctiva bears some relationship to trachoma, but the disease could not be diagnosed either clinically or microscopically in these 2 patients.

The authors suggest that this disease may not be as rare as reported in the literature, particularly in areas in which trachoma is common. They suggest that specimens for microscopic examination be taken from the lesions of all patients who have hypertrophy of the tarsal plate and conjunctiva, for determination of the presence or absence of amyloidosis.—*Thomas P. Kearns, M.D.*

25. *Some Observations in Entropion and Ectropion and a Method of Conjunctivo/rhinostomy.* R. BRUCE RAMSEY. Bull. Acad. of Med., Toronto 33:102–105, March, 1960.

In this technique, a Kuhnt-Szymanowski procedure is done, but the excised skin is used in the form of a free full-thickness graft to relax the vertical tension.

When the lacrimal sac has been destroyed, a thin mucous membrane graft is sutured, raw side out, to a polyethylene tube and placed in a track between the conjunctiva and the nose. 7 references.—*Clement McCulloch, M.D.*

MEDICAL OPHTHALMOLOGY

26. *Evaluation of Ocular Signs and Symptoms in Myasthenia Gravis.* N. S. SCHLEZINGER AND W. A. FAIRFAX. A.M.A. Arch. Ophth. *62*:985–990, 1960.

A brief survey of the historical development of current knowledge of myasthenia gravis is presented along with a survey of 52 patients first seen by an ophthalmologist.

The age incidence varied from 18 months to 75 years. Attention is called to a congenital form of the disease characterized by a symmetrical, bilateral external ophthalmoparesis. In the group there were 32 men and 20 women. Of 50 patients observed for a three-year period, 16 (or 32 per cent) had ocular myasthenia gravis, while 34 (or 68 per cent) had generalized myasthenia. Thirty-eight of the 50 patients had involvement limited to the eyes on initial examination, but within three years, 20 of these developed generalized myasthenia gravis. The "ocular" group of 16 supports the concept that after two or three years, it is likely that myasthenia gravis limited to the eyes will remain ocular and therefore constitute a relatively slight threat to the life of the individual.

The onset was insidious in the vast majority of these cases, and initial manifestations involved more than one extraocular muscle. Eleven of 12 patients who had only one eye involved at the time of initial examination were followed for one

year and 7 continued to have involvement limited to this one eye. Three patients revealed concurrent hyperthyroidism and myasthenia gravis. Treatment consisted mainly of either neostigmine or pyridostigmine, usually combined with ephedrine unless contraindicated. Only partial subsidence of the extraocular involvement was obtained in many cases. ACTH therapy is stated to be highly effective ordinarily in reducing or eliminating the extraocular muscle pareses when these are relatively refractory to neostigmine or pyridostigmine medication.—*Garrett L. Sullivan, M.D.*

27. *Neuro-ophthalmologic Evaluation of Abducens Nerve Paralysis.* E. C. SHRADER AND N. S. SCHLEZINGER. A.M.A. Arch. Ophth. *63*:84–91, 1960.

One hundred and four cases of isolated sixth nerve paralysis, initially seen by an ophthalmologist, are analyzed from the standpoint of diagnosis and prognosis. In nearly half the cases, no conclusive diagnosis could be made. Diabetes mellitus accounted for 15.4 per cent, with the youngest patient being 50. Among this group of 16 cases, the diagnosis of diabetes was made in 7 as a result of the sixth nerve paralysis. Average duration of the paralysis was three months. Multiple sclerosis was the cause in 12.5 per cent of the series. In this group only 1 patient was older than 45 years and the average duration of paralysis was 10 to 11 weeks. Abducens paralysis proved to be the initial manifestation of multiple sclerosis in 7 of these 13 patients. Syphilis was the etiological agent in approximately 10 per cent of the series, with complete recovery on penicillin therapy being achieved in those cases where the paralysis was less than 10 weeks in duration. Neoplasm, neuritis, trauma, and miscellaneous causes were found in 18 patients. Special mention is made of the absence in the series of any proved case of aneurysm. Of the 45 per cent of patients in whom the etiology was undetermined, systemic arteriosclerosis and hypertension were present in 22 and multiple sclerosis was suggested in 7. There were 10 cases in which no possible etiological factor could be ascertained.—*Garrett L. Sullivan, M.D.*

28. *Ocular Complications in Sickle-Cell Hemoglobin C Disease.* S. MUNRO AND C. WALKER. Brit. J. Ophth. *44*:1–24, 1960.

The authors present a review of the literature concerning this and allied hemoglobinopathies and then report their observations on 9 cases. The retinopathy of sickle-cell hemoglobin C disease is confined mainly to the periphery, and the characteristic appearances are the following: arteriovenous anastomotic communications with terminal bulbous or varicose dilatations; brushlike terminations of the peripheral retinal capillaries and new vessel formation; peripheral areas of choroidretinal atrophy; peripheral fibrosis; curious "red" areas, which have been ascribed to thin preretinal or subretinal hemorrhages; thrombosed peripheral retinal veins; and exudative retinal detachment, vitreous hemorrhage, uveitis, and cataract. The retinopathy may be present without any diminution of the visual acuity.

All 9 patients reported exhibited these retinal findings in varying degree and 7 were proved by electrophoresis to have sickle-cell hemoglobin C disease.

In all cases both eyes were involved. Treatment of ocular complications is un-

satisfactory. Prophylactic diathermy to the anastomotic capillary networks, to prevent vitreous hemorrhage, is suggested.—*Garrett L. Sullivan, M.D.*

29. *The Pathology of Mikulicz-Sjogren Disease in Relation to Disseminated Lupus Erythematosus. A Review of the Autopsy Findings and Presentation of a Case.* GORDON O. BAIN. Canad. M.A.J. *82*:143–148, Jan. 16, 1960.

Mikulicz' disease and Sjögren's syndrome may be regarded as varying clinical expressions of the same underlying disease process. The specific lesion found in the lachrymal gland may occur as an isolated mass in a major salivary gland or as multiple lesions in major and minor salivary glands. The condition may be seen accompanied by xerostomia, arthritis, and a variety of other concomitants. The lesions in these glands are remarkably similar to those found post mortem in systemic lupus erythematosus. There are morphological similarities between the changes in Mikulicz-Sjögren's disease and in the thyroid lesion of Hashimoto's struma. In view of experimental work on the autoimmunological pathogenesis of Hashimoto's disease, a similar mechanism may be suggested for Mikulicz-Sjögren's disease. Such a mechanism may apply to other hyperergic diseases, including lupus erythematosus. 5 figures. 1 table. 39 references.—*Clement McCulloch, M.D.*

30. *Local Administration of Anticholinesterase Agents in Ocular Myasthenia Gravis.* I. H. LEOPOLD, T. R. HEDGES, JR., J. MONTANA, N. KRISHNA, AND S. BECKETT. A.M.A. Arch. Ophth. *63*:544–547, 1960.

Myasthenia gravis is of considerable ophthalmological interest because the initial symptoms are usually found in the extraocular muscles. Therapy is dependent on the use of systemic neostigmine as well as other anticholinesterase agents. Seven patients treated with local neostigmine and demecarium bromide are presented. There was sustained improvement of function in 5 cases, a transitory effect in 1 case, and no improvement in 1 case. Ptosis appeared to be particularly relieved. Three of 4 patients tested demonstrated electromyographic evidence of improvement. Local side effects, such as miosis, ciliary spasm, headache, and difficulty in accommodation, were also present to some degree.—*Ralph Z. Levene, M.D.*

31. *Emotional Glaucoma.* M. CROLL AND L. J. CROLL. Am. J. Ophth. *49*:297–305, 1960.

Three cases of "emotional" acute glaucoma are presented. All followed major surgery, which precipitated a severe emotional upset. The patients were unstable, emotionally immature, and belonged to a separate personality group. The predisposing factor was a shallow anterior chamber. The exact ocular pathogenesis in precipitation of the acute attack is not fully understood.—*Ralph Z. Levene, M.D.*

32. *Experimental Diabetic Retinopathy.* A. DE ROETTH, JR., AND Y. F. PEI. A.M.A. Arch. Ophth. *63*:226–231, 1960.

Since the pathogenesis of diabetic retinopathy is unknown, an experimental

approach to the problem was undertaken. The in vitro retinal metabolism of rats with alloxan-produced diabetes was compared with that of a normal group. There was a lower rate of anaerobic glycolysis in the alloxan-treated rats. Oxygen consumption depended on the substrate. With a glucose substrate, no difference was noted between the two groups; with a succinate substrate, the diabetic group showed a greater oxygen consumption; and with pyruvate, both groups showed an increased oxygen consumption.—*Ralph Z. Levene, M.D.*

33. *Ocular Findings in Cystic Fibrosis of the Pancreas.* G. M. BRUCE, C. R. DENNING, AND H. F. SPALTER. A.M.A. Arch. Ophth. *63*:391–401, 1960.

Cystic fibrosis of the pancreas is a hereditary disease of children and young adults characterized by dysfunction of many of the exocrin glands. It is manifest most often by pancreatic insufficiency, chronic lung disease, and excessive loss of sodium and chloride in sweat. The etiology is unknown. Ophthalmological abnormalities in 24 cases are presented. The characteristic findings in all patients were varying degrees of venous engagement and edema of the disc. Hemorrhages and cystic macular changes occurred in some cases. Investigation into the etiology of the abnormal eye findings disclosed only two constant relevant factors: the presence of moderate to severe pulmonary disease and elevation of the gamma globulin levels in the serum and cerebrospinal fluid. However, the mechanism by which eye changes develop is far from clear.—*Ralph Z. Levene, M.D.*

34. *The Probable Role of Benign Histoplasmosis in the Etiology of Granulomatous Uveitis.* A. C. WOODS AND H. F. WAHLEN. Am. J. Ophth. *49*:205–220, 1960.

Systemic histoplasmosis, although rare as a fatal disease in man, is quite common as an unsuspected and asymptomatic infection, especially in certain areas. The diagnosis can be made only by an unexplained pulmonary calcification, hypersensitivity to histoplasmin, or on some other similar serological or immunological response. In evaluating the role of histoplasmosis in uveitis, the authors studied 186 patients with granulomatous uveitis and 107 patients with nongranulomatous uveitis. There was an increased incidence of positive histoplasmin reaction in patients with granulomatous uveitis as compared with those with nongranulomatous uveitis and with the normal population. Of the 62 positive reactions to histoplasmin, 19 showed a peculiar and consistent fundus lesion. Nine of these patients showed the trilogy of histoplasmin sensitivity, pulmonary calcification, and anergy to tuberculin. Based on this evidence, it appears reasonable to assume a cause-and-effect relationship between a benign systemic histoplasmosis and the ocular reactions. —*Ralph Z. Levene, M.D.*

Questions and Answers

Q. *A 36-year-old woman has chronic lid edema. What is the approach to this problem?*
A. Systemic causes, such as thyroid dysfunction and kidney disease, should be excluded. Then, local causes, such as allergy, chronic lid infection, and refractive error, should be investigated.

Q. *A male patient, 56 years of age, has vision correctible to 20/20 in the right eye and to 20/200 in the left eye. The impaired vision in the left eye is due to an immature cataract. Should cataract extraction be advised in the left eye?*
A. Each case of this type should be decided on its individual merits. The ophthalmologist's decision will be influenced by the systemic health, visual needs, and attitude of the patient. In most cases, cataract extraction would be advised as adequate binocular vision can be obtained by the use of corneal lenses in the aphakic eye.

Q. *Does a cataract have to be "ripe" before cataract extraction is done?*
A. Before the advent of intracapsular cataract extraction, the surgery was done more easily and successfully if the cataractous crystalline lens was mature. However, in intracapsular cataract extraction, which is presently the preferred procedure, immature cataracts can be removed with more relative ease than mature (ripe) or intumescent cataracts.

Q. *What persons can wear contact lenses?*
A. Most patients with refractive errors can wear properly fitted corneal contact lenses. They are especially recommended in patients with myopia, aphakia, irregular corneal astigmatism, and keratoconus.

Q. *A 4-year-old child has intermittent exotropia. What is the treatment?*
A. The treatment of choice is surgical correction of the strabismus. Postoperative orthoptics is a useful adjunct in individual cases.

Q. *A patient has a pterygium encroaching on the cornea for approximately 3 mm. Should it be surgically excised?*
A. While a pterygium of this size may remain inactive for years, it may be subject to sporadic episodes of growth at any time. As inactive and small pterygiums are removed with less difficulty than larger and actively growing ones, it is best to remove them for this reason and for cosmetic purposes.

Q. *A 9-year-old child frequently twitches his lids, and on occasion he "jerks" his eyes to the left. Is this a nervous habit?*
A. While such a phenomenon may be due to a tic, the diagnosis should be made only after exclusion of organic causes, such as external eye pathology. A frequent

---

NOTE: Questions from readers are invited. Address Dahar Cury, M.D., 2665 Walnut St., Huntington Park, Calif.

local cause is vernal catarrh or refractive error. Chorea may cause similar symptoms. Focal seizures must be excluded by electroencephalography and a neurological examination.

Q. *Can diabetic retinopathy develop before glycosuria is present?*
A. Unfortunately, this can happen. Usually, such patients have an abnormal glucose tolerance curve, and subsequently, they will develop classical diabetes mellitus.

Q. *A 58-year-old man suddenly developed left sixth nerve paralysis. How should he be managed?*
A. A careful diagnostic investigation should be done to exclude intracranial and orbital causes such as tumor, aneurysm, or other neurological disease. In many cases, no organic cause can be determined and focal neuronitis is presumed to be the cause of the isolated nerve paralysis. Patching will relieve the patient of the bothersome diplopia. After approximately six months from the onset, if no organic lesion has developed, muscle transplantation should be seriously considered.

Dahar Cury, M.D.
Huntington Park, Calif.

Pan American Association of Ophthalmology Holds Sixth Official Congress

Dr. Jorge Valdeavellano, Lima, Peru, was elected president of the Pan American Association of Ophthalmology at the Sixth Quadrennial Congress held in Caracas, Venezuela, January 31 to February 6. Dr. Valdeavellano succeeds Dr. Brittain F. Payne, New York City.

Vice-presidents elected were Dr. Mark R. Marshall, Edmonton, Alberta, Canada; Dr. Alfonso Gaitan Nieto, Bogotá, Colombia; and Dr. Julio Raffo, Lima, Peru.

Dr. Benjamin Boyd, Panama City, republic of Panama, was elected executive director of the association to succeed the late Dr. Moacyr E. Alvaro, São Paulo, Brazil, and Dr. Renato de Toledo, São Paulo, was elected executive secretary for countries south of Panama, succeeding Dr. Jorge Balza, Buenos Aires, Argentina.

Lima, Peru, was chosen as the place for the next interim congress in 1962, and Montreal, Quebec, Canada, for the next official congress in 1964.

Dr. Payne was honored at the opening session of the congress when the Gradle Medal was awarded to him in recognition of his outstanding excellence in graduate and postgraduate teaching.

Dr. Conrad Berens, New York City, a former president of the association and editor of the Quarterly Review of Ophthalmology, received the association's medal for noteworthy contributions to the prevention of blindness in the Western Hemisphere. The presentation was made at the closing ceremony of the congress on Saturday, February 6.

A New MD Medical History...

A HISTORY *of* OPHTHALMOLOGY

by George E. Arrington, Jr., M.D.

Associate in Ophthalmology, Medical College of Virginia, Richmond, Virginia

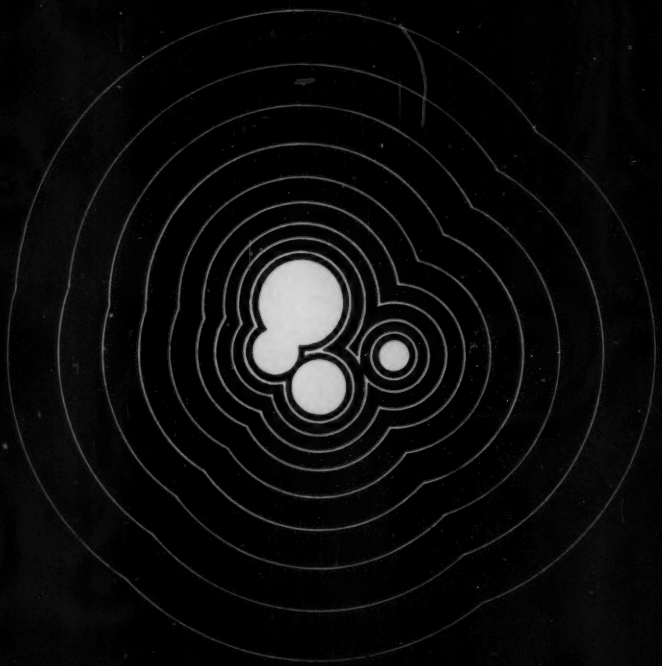
A HISTORY OF OPHTHALMOLOGY provides an over-all view of ophthalmological progress through the ages. With scholarship and originality the author traces the thinking, of men known and unknown, that has made possible the technological advances of this science. Man's search for understanding of vision and its preservation is shown effectively in its relation to the history of civilization. The content of this book ranges from the period of prehistorical ophthalmology to the present day. In emphasizing the effect of related sciences, philosophy, and human culture upon ophthalmology, Dr. Arrington offers new insight into his subject. Appropriate attention is given the ascendancy of modern ophthalmology including an evaluation of its current trends in the light of the future. It is a book of interest to ophthalmologists, general practitioners, and students.

This volume is one of a series devoted to the histories of various specialties and facets of medicine. Félix Martí-Ibáñez, M.D., who wrote the foreword to A HISTORY OF OPHTHALMOLOGY, is the Editorial Director of the series, which includes books on Public Health and Neurology.

192 PAGES / $4.00 / CLOTH BOUND

MD PUBLICATIONS, INC.

30 EAST SIXTIETH STREET, NEW YORK 22, NEW YORK

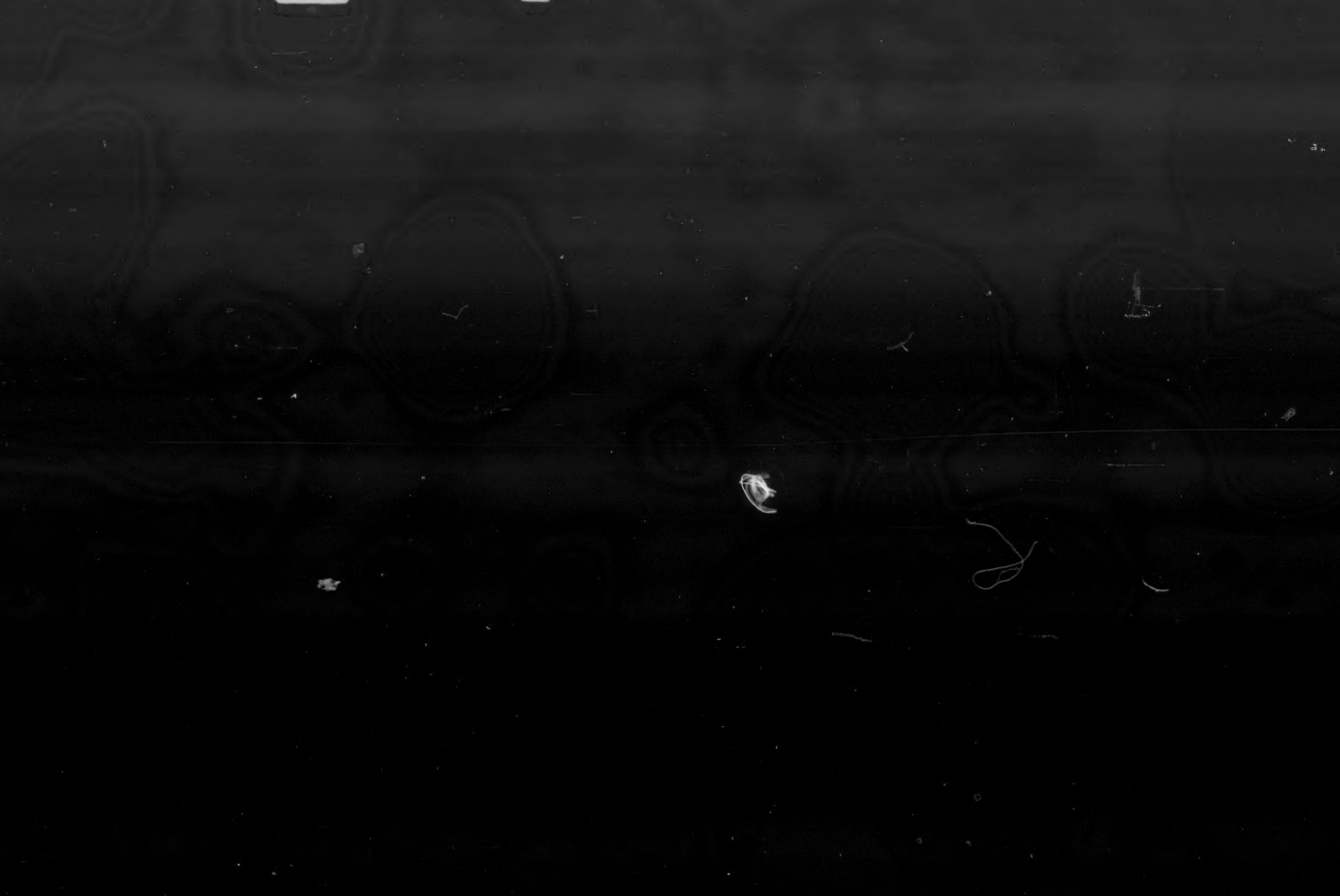


THE DRAMATIC STORY OF THE ANTIBIOTIC MIRACLE

the antibiotic saga

by Henry Welch, Ph.D.
and Félix Martí-Ibáñez, M.D.

This is the epic tale of the "wonder" drugs that have changed the course of modern medicine and shed new light on man's age-old struggle against disease. It is the first book to tell with color, clarity, and accuracy the story of **all** antibiotics and the history of their use **before** their official discovery by Fleming. This compelling story has its origin in the age of the Pharaohs and ranges through time and space, retracing from the present day the intricate pattern of antibiotic development. Broad in scope, THE ANTIBIOTIC SAGA covers not only the broad-spectrum antibiotics but the newer, less known drugs that are the result of the dedication and efforts of the acknowledged great – Fleming, Pasteur, Tyndall, Ehrlich – and the heroic unknown. THE ANTIBIOTIC SAGA is a fascinating book, a great tribute to the men who contributed to this historic tale and to those who continue, daily, to meet the many challenges of the unfinished antibiotic drama.

150 PAGES / CLOTH BOUND / $3.00

MEDICAL ENCYCLOPEDIA, INC.
30 EAST 60TH STREET, NEW YORK 22, NEW YORK